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OF

THE JOHNS HOPKINS HOSPITAL

Entered as Second-Class Matter at the Baltimore, Maryland, Postoffice.

[Vol. XXI.—No. 232.] BALTIMORE, JULY, 1910. Price, 25 Cents

CONTENTS.

PAGE

A Unique Coincidence of Multiple Subcutaneous Hæmangio-Endothelioma, Multiple Lymphangio-Endothelioma of the Intestinal Tract and Multiple Polypi of the Stomach Undergoing Malignant Changes; Associated with Generalized Vascular Sclerosis and Cirrhosis of the Liver. (Illustrated.)
By M. C. Winternitz, M. D., and Thomas R. Boggs, M. D. 203

A Review of the Recent Advances in our Knowledge of Tropical Diseases.
By John L. Todd, M. D. 212

PAGE

Anaphylaxis and Its Relation to Clinical Medicine.
By John F. Anderson, M. D. 218

An Unusual Case of Cerebral Tuberculosis Following Tuberculous Otitis Media. (Illustrated.)
By H. O. Reik, M. D. 223

Etiology of Chronic Arthritis.
By Herman W. Marshall, M. D. 226

Notes on New Books 230

Books Received 232

A UNIQUE COINCIDENCE OF MULTIPLE SUBCUTANEOUS HÆMANGIO-ENDOTHELIOMA, MULTIPLE LYMPHANGIO-ENDOTHELIOMA OF THE INTESTINAL TRACT AND MULTIPLE POLYPI OF THE STOMACH UNDERGOING MALIGNANT CHANGES; ASSOCIATED WITH GENERALIZED VASCULAR SCLEROSIS AND CIRRHOSIS OF THE LIVER.

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Introduction.

The basis for the following histological studies with the theoretical deductions appended is found in a case which has been under clinical observation for the past three years. This showed such unusual features during life that we undertook an exhaustive investigation of the tissues at autopsy.

The material will be presented in the following order:

1. Description of the case.
2. Protocol of the autopsy.
3. Histological studies.
4. Summary and theoretical deductions.

Clinical History.

T. H., male, mulatto, 65 years old. Ship's cook. Born in Hindustan. Was admitted to the Johns Hopkins Hospital, November 17, 1906. Medical number 20,395.

Complaint: "Swelling of stomach."

Family History: Unimportant.

Personal History: Patient had measles as a child, smallpox at 9. He does not recall having had any other diseases in childhood. Has never had typhoid fever, pneumonia, or pleurisy.

No cardiac or respiratory symptoms.

Gastro-Intestinal: Patient has always had a good appetite. His bowels have moved once a day regularly. He has never had any colic or pain in the abdomen. About 20 months ago, after quitting drink, he began to have occasional attacks of vomiting in the morning. The vomitus was yellow and tasted very bitter. He has had similar attacks (one every 2 to 3 weeks) up to the present. Has not noticed blood in his stools.

Urinary: Patient has slight nycturia, but never has had any burning or pain on micturition. Patient denies having

had syphilis and gives no definite history of a hard or soft chancre. No history of secondaries. Gonorrhœa at 17.

Skin: Patient has never been jaundiced. He has never had any skin eruption, or itching.

Extremities: No ulcers on legs. No pain in joints or bones.

Habits: Patient's work has always been light—cooking on shipboard, and serving in army and navy. *Alcohol:* Up to two years ago patient was a steady drinker. When on shore he drank 3 to 4 glasses of beer a day and half a pint to a pint of whiskey. He got no liquor while at sea, but went on a spree whenever in port. Two years ago he quit drinking entirely, and has not used alcohol since. *Tobacco:* Practically none.

Present Illness: About 3½ months ago, while working in a store, he noticed swelling of the feet. At this time he had to walk a great deal. The swelling got worse during the day, but subsided at night. Gradually his "stomach" became swollen, and the œdema of the legs remained constant. About 2½ months ago he quit work for a week or so, rested, and took large doses of Epsom salt. He states that his stools were of clear, watery fluid. The ascites subsided, and he went back to work, at which he continued till 10 days before admission. His only symptom has been abdominal swelling. His bowels have moved once a day. A few times he has vomited a little bitter yellow fluid in the morning. This contained no blood. He has not noticed any blood in his stools. His appetite has been good. His micturition has been as usual. He has had no palpitation or shortness of breath till recently, when he has had dyspnœa on exertion. He has had no cough. Has not lost weight.

Physical Examination: The patient is a light mulatto, sparely nourished. There is no exophthalmos. Pupillary reactions are normal. Gums and mucous membranes show slight cyanosis. Thyroid isthmus is slightly enlarged; the lobes are barely palpable. Lymphatics of the neck seem normal. Respirations are shallow and costal in character; expansion is limited on both sides. Percussion note is hyperresonant over the upper lobes in front with dulness low in the axillæ and in both backs. The breath sounds are harsh and clear over the upper lobes, diminishing over the impaired area and accompanied by numerous fine moist râles on forced inspiration. No evidence of fluid in the pleura.

Heart: Displaced upward. Point of maximum pulse in 4th left interspace 10.5 cm. from mid line. Dulness reaches 13.5 cm. to left in 4th interspace and above to 1st interspace, 2.5 cm. to right in 3d interspace. The heart sounds are clear and regular and of normal intensity. The pulse is 80, regular in force and rhythm, of moderate tension, with very marked sclerosis of the peripheral arteries.

Abdomen: The abdomen is very tense and swollen; its skin is shiny. The superficial veins are enlarged, especially those along the lateral margins. There is no caput medusæ. Epigastric veins are not prominent. Umbilicus is protruding. Fluctuation wave is definite. Liver not palpable. Spleen not felt. There is movable dulness on percussion. The liver dulness begins at the 3d rib and extends to point 3.5 cm. above the costal border in the right mammillary line. The girth of the abdomen at umbilicus is 106 cm.

Genitalia: Normal except for an atrophic undescended left testicle.

Extremities: There is marked clubbing of the fingers and toes. There is œdema of the thighs and legs. The knee kicks are normal. Plantar response is normal.

Nov. 19: Abdomen tapped and 7.5 litres of straw-colored fluid removed from the abdominal cavity. Nothing remarkable about the appearance on microscopic examination of this material. The cellular elements were few. Specific gravity, 1011; albumin, 6.6 grams per litre.

Blood: Showed secondary anæmia. R. B. C., 4,492,000; W. B. C., 5400; Hb., 82 per cent.

Differential Count: Showed slight reduction of the polymorphonuclears and small mononuclears. Slight increase in large mononuclears and transitionals.

Patient was much relieved by the removal of the ascitic fluid. The edge of the liver could not be made out definitely. Spleen was not palpable.

Patient was tapped again on Nov. 30 and 5.5 litres removed. From this time he gradually improved and was discharged Dec. 17, 1906.

2d admission, March 23, 1907: Patient was readmitted in much the same condition as before. In the three months since he left the hospital he had been unable to work and has had some occasional morning vomiting and gradually increasing ascites, anasarca, and dyspnœa.

Physical Examination: Is practically as on first admission, except that on admission it was noted the peripheral arteries, generally, and the veins, as well, were very greatly thickened. The anæmia had somewhat increased, hæmoglobin being 62 per cent, 5000 white cells, and 4,000,000 red cells. The great distension and dyspnœa were relieved by tapping and removal of 10 litres of ascitic fluid.

After repeated tappings, patient's condition gradually improved. The edge of the liver is noted as palpable on June 10, small, smooth and hard.

Patient was discharged on June 15, somewhat improved.

3d admission, Sept. 16, 1907: Patient was confined to his bed much of the time between his discharge from the hospital and readmission with the same symptoms as before; marked ascites, swelling of the legs, dyspnœa, occasional nausea and vomiting. No blood in the vomitus nor stools.

Physical Examination: Practically as on previous notes, except for some increase in cyanosis. The girth was 112 cm. on admission; 86 cm. after tapping and removal of 11 litres of straw-colored fluid. Character of the fluid practically the same as previously noted.

Dr. Emerson, Nov. 14: A few small nodules along the right forearm which suggest phleboliths; not attached to any vein.

The edge of liver is distinctly palpable after tapping. The liver seems very small. The lateral abdominal veins are large with a distinct upward current in them. There is a slight enlargement of both parotid glands.

On Dec. 19 it is noted that the skin on the lower arms

shows marked wrinkled lines suggesting ichthyosis. A small firm subcutaneous nodule is found above the left scapula.

Patient discharged at his own request, slightly improved, Dec. 19, 1907.

4th admission, Feb. 3, 1908: Patient spent the intervening time in bed. Has been very comfortable. The increase in ascites and shortness of breath forced him to return to the hospital.

Physical Examination: Practically as in previous admissions.

Dr. Thayer: Increase in the clubbing of the fingers, palpable small liver and enlarged spleen. Parotid enlargement increased. Moderate dilatation of the superficial veins of the abdomen and thorax. No *caput medusæ.*

Patient improved under treatment after repeated tappings and was discharged on April 21, 1908.

Diagnosis: Cirrhosis of the liver (atrophic).

5th admission, June 16, 1909: In four weeks, since his discharge, patient has gradually become œdematous and the ascites is very marked. Some dyspnœa and morning vomiting.

Physical Examination, Dr. Clough, June 18, 1908: Emaciated. Skin dry, scaly, of a peculiar chocolate color. Scleræ distinctly jaundiced. Marked arcus senilis. Mucous membrane of mouth distinctly pale.

Lymph glands are somewhat enlarged, firm and shotty throughout. Both epitrochlears felt.

Chest flaring. Movements rather shallow and restricted. Lungs clear throughout on percussion. Breath sounds vesicular throughout. Numerous crackles at bases and lower axillæ.

Heart: Displaced upward. Sounds clear throughout, normal in character.

Pulse regular, fair in volume, tension not increased. Brachial and radial arteries markedly tortuous, visible; diffusely sclerotic.

Abdomen: Much distended, bulging in flanks. Veins are distended. On palpation very tense—nothing can be felt. No tenderness. Marked fluctuation wave. On percussion, tympany in epigastrium and upper abdomen. Movable dulness in the flanks.

Legs are moderately œdematous.

Oct. 27, 1908: R. B. C., 4,270,000; W. B. C., 8600; Hb., 53 per cent.

Dr. Boggs, Nov. 3, 1908: Scattered along the inner aspect of right upper arm and forearm, and somewhat on ulnar side of forearm, are several subcutaneous nodules, of fairly uniform size, averaging about 5 mm. in diameter. They are quite firm in consistency, the skin moves freely over them, and they are more or less adherent to the fascia, though some of them can be picked up in fingers and moved freely. No pain on pressure over them. On stretching the skin tightly over them, they are seen, in good light, to have a faint blue color, similar to that of the veins. There are a very few similar nodules on the left forearm, mostly on its ulnar aspect; none on the upper arm. There are a few, also, scattered about the back, at the right scapular angle and along the spine. No nodules felt in skin of lower legs.

Dr. Boggs, Nov. 18, 1908: The larger subcutaneous nodules noted in the arms, apparently have pulsation on picking them up. The subcutaneous tissue in lower leg is somewhat œdematous and no nodules can be made out. About the popliteal space on both sides are a few small nodules, corresponding in size and texture to those noted in the arms. No nodules made out in the back, which is œdematous.

On costal border are two small angiomata symmetrically placed, just above costo-chondral articulation of 6th rib on each side.

Dr. Boggs, Dec. 24, 1908: The subcutaneous angiomata have increased in size especially on right forearm. Under local anæsthesia an attempt was made to excise one of the subcutaneous nodules at junction of mid and lower third of right arm. On exposure it seemed to have a deep purple color and lay parallel and in close relation to a small cutaneous artery. On attempting to free it from surrounding tissues, the capsule was punctured and the small tumor collapsed, leaving an actively pulsating arterial lesion. This wound was closed, as the tumor could no longer be recognized, and a second node on inner side of elbow was excised with artery lying parallel to and supplying it. It was placed in Zenker's fluid for microscopic examination. This mass, when exposed, seemed to be a direct offshoot of a very sclerotic artery.

Dr. Boggs, Feb. 3, 1909: The small angioma, which collapsed on attempted excision Dec. 24, has filled up and presents the same picture as before. The number of nodules somewhat increased, especially along extensor surface of forearm on both sides.

Dr. Boggs, April 21, 1909: Patient continues to fill up rapidly after tapping. General condition otherwise much the same. The clubbing of fingers is perhaps more marked than on admission. Wassermann reaction, negative.

Dr. Boggs, June 5, 1909: The subcutaneous angiomata are increasing in size and number on both arms. A new one, in the right hand at middle of the ulnar margin, shows some redness in skin over it. Another, not previously noted, at base of first finger and near it a marked ecchymosis.

Patient's general condition is very much as in last note. Parotid glands are rather more swollen, have a soft induration, and are not tender.

Dr. Brotherhood, June 10, 1909: 33d tapping. 9 litres of straw-colored fluid removed, slightly cloudy. Reaction neutral. Specific gravity 1012. Albumin—Esbach, 3¾ grams per litre. Microscopically—contains few endothelial cells, few mononuclear leucocytes.

Dr. Boggs, June 21, 1909: Few scattered subcutaneous nodules on the legs similar, on palpation, to those noted on the arms, but smaller. One or two small ones felt about popliteal spaces on both sides.

Dr. Sladen, Aug. 5, 1909: To-day there are two fairly good-sized nodules just over right zygoma, not previously noted. Two new ones on right wrist, and over arms and face are many small red macules from which the blood is easily expressed, which suggest new formed angiomata.

Dr. Futcher, Sept. 10, 1909: Patient has not been so well for the past few days. The bowels, which have been rather

loose throughout, have been more so in the past three days, as many as ten stools a day. Forearms, particularly over the ulnar aspect, present numerous subcutaneous visible and palpable nodules, ranging from 0.5 to 1.5 cm. There are probably 20 to 30 on each arm. Skin is movable over them and they are movable on subjacent structures. They appear to be situated chiefly along the course of subcutaneous veins, often being observed at junction of two veins. They are fairly firm —do not diminish materially in size on pressure.

Dr. Boggs, Sept. 13, 1909: Emaciation has progressively increased. The angiomatous nodules under skin of arms have increased in size and number, and color shows through skin. Many of them have a reddish-purple tint. Forearms are quite thickly studded with these nodules. A few are found on wrists and dorsa of the hands—none on the fingers. There has been no appreciable increase in number of the nodules about the shoulder girdle. None are found on the back. A few small ones are found about the iliac crests and over the sacrum, which were not noticeable eight weeks ago. There are a few of these similar nodules, quite small, but palpable, on the inner side of the thigh along the course of superficial veins. There is a group of nodules, not larger than wheat grains, just below the popliteal space and a few along the course of the long saphenous vein on the right side. On the left leg the nodules in the thigh are slightly more numerous than on the right, and larger. Distribution on the left leg is quite similar to that on right. None made out on dorsum of foot.

Dr. Boggs, Oct. 6, 1909: The number of the subcutaneous nodules is increasing, the skin over some of the larger is becoming more atrophied, and color shows through quite distinctly, either reddish or purplish. The small nodules on legs are also increasing in number and size. General condition otherwise much as before.

Oct. 16, 1909: Abdominal tapping No. 43. 8150 cc. of pale yellow, turbid fluid removed. Specific gravity 1008. Reaction neutral. Albumin 6 grams per litre. Endothelial cells, with eccentric nuclei and granular cytoplasm.

Blood Examination, Oct. 22, 1909: R. B. C., 3,940,000; W. B. C., 11,800; Hb., 50 per cent.

Dr. Boggs, Dec. 12, 1909: Patient has gradually sunk into coma with respirations taking on a true air-hunger type. The ascites has disappeared. The skin is wrinkled and loose over the abdomen. There is œdema of the hands and dependent portions of the body, moderate in grade, with numerous subcutaneous hæmorrhages into deeper layers of the skin, varying from petechiæ of small size to several centimeters in diameter. Breath has rather a fruity odor. The dessicated condition of the skin has brought into prominence some small nodules not previously noted, having the same character as those described on the arms. There are several masses on the face above the zygoma, above the tragus, a third just below the right malar; none made out on left side of face.

Some impairment of respiration movements in both bases behind and deep inspiratory movements are accompanied by showers of rather dry râles. Nowhere is any tubular breathing made out. Along the left border of the heart there are showers of dry crackling râles at the end of inspiration. Heart sounds are distinct and feeble.

Liver dulness begins at rib vi, extends only about 4 cm. in mammillary line. Neither liver nor spleen is felt. Small subcutaneous nodules, noted in legs, have increased in size, apparently involving the skin, and differ from others in showing fine radiating vessels about margin, of bright red color. They are very hard and shotty. There is slight œdema of thighs and also of lower leg. The ichthyosis is very marked.

Dec. 15, 1909: The coma persisted and the patient became gradually weaker and died at 9.10 a. m.

During this last admission 432 litres of fluid were drawn from abdomen in 47 tappings. This represented a protein loss of 260 grams.

Diagnosis: Atrophic cirrhosis of liver; multiple subcutaneous hæmangiomata; ichthyosis simplex. Chronic gastritis and colitis.

Autopsy.

T. H., aet. 67 years. Ward M. Died 9.10 a. m., Dec. 15, 1909. Autopsy (No. 3310) 9.30 a. m., Dec. 15, 1909. Dr. Winternitz.

Anatomical Diagnosis: Cirrhosis of liver; ascites; chronic proliferative peritonitis; collateral circulation established through the diaphragm to the lungs and through the omentum to the parietal peritoneum; arterio-sclerosis with diffuse dilatation of the aorta and thrombus formation; sclerosis of the peripheral arteries and veins with multiple subcutaneous and visceral hæmangiomata undergoing malignant change (endothelioma); multiple lymph-angiomata of the intestine and stomach undergoing similar change; chronic gastritis with multiple polypi undergoing carcinomatous degeneration; chronic fibrous myocarditis; pulmonary emphysema; chronic fibrous pleurisy; chronic interstitial and peri-splenitis; chronic diffuse nephritis.

Only those portions of the protocol which have a bearing upon the subsequent investigations will be given in detail.

Body: Is that of a somewhat emaciated mulatto man, 173 cm. in length. Rigor mortis has not yet set in, and there is no lividity even in the dependent parts. The face is somewhat emaciated and both temporal fossæ are conspicuous and the orbits are somewhat depressed. The conjunctivæ are slightly pigmented about the periphery of the corneæ. The pupils are equal and measure about 4 mm. in diameter. There is a slight arcus senilis. The thorax is barrel-shaped. The abdomen is scaphoid. The veins over the abdomen are rather more prominent than normal. In the median line beneath the umbilicus is a non-pigmented scar-like area.

Perhaps the most noteworthy thing on external examination is the presence of numerous small, subcutaneous nodules (Fig. 1); these have been described in detail in the history. The nature of these nodules in general is as follows: They are elevated and vary somewhat in their consistence, some being extremely firm and shot-like; others not quite so firm, and a few can be decreased markedly in size on pressure. They are

all of them freely movable on the underlying tissue. In a few the skin is slightly adherent. These tumors vary in size; the largest ones measuring about 1 x .75 x .75 cm., while small ones occur which are almost miliary in size. Their distribution is somewhat as follows: On the right side of the head just above the zygoma; in the region of the temporal veins above the orbit; beneath the malar process; and a small one just anterior to the tragus. The left side of the face seems to be free from tumors, and none are to be made out in the neck. On the trunk the tumors are scanty and irregular. There are none on the anterior wall and axillæ with the exception of a single node in the middle of the left upper abdominal quadrant. On the back there are a few nodules about the right scapula and some large ones in the sacral and gluteal regions. Scattered over the arms and legs, in general parallel to the course of the subcutaneous vessels, are many nodules, the larger being confined to the upper extremities, while those in the legs are somewhat smaller and softer. The relation of these tumors to the vessels can be much more distinctly seen on subcutaneous examination. On reflecting the skin there is found an extreme diffuse thickening of the subcutaneous veins. Over the outer half of the elbow and the upper third of the forearm a number of small, nodular masses are found lying in the superficial fascia. These masses correspond in general appearance to those previously excised and described during life and vary in size from about 6 x 4 x 3 mm. to scarcely more than a pin-head. The larger ones are dark red in color and firm in consistence, having a well-defined capsule. The smaller are rather translucent, very much paler in color and firmer in consistence. Although these are very superficial in position they have nowhere invaded the skin proper, and in some places the injection[1] of small capillaries in the skin over the tumors involves the capsule of the tumor, but not the tumor itself. In position these masses have a striking relation to the small branches of the superficial veins. In general they lie parallel to the larger veins and small branches diverge toward them from these trunks. At one point, where the deep layer of fascia has been cut, a small tumor nodule is found lying in the fascia between the muscles, but not invading the muscle.

Abdomen: Contains an excess of clear yellowish fluid. The omentum is rolled up, thickened, and extensively adherent to the parietal peritoneum, especially in the left upper quadrant, and the adhesions are almost entirely composed of vessels averaging 2 to 3 mm. in diameter. Numerous hæmorrhagic areas are scattered through the omental fat. The dome of the right lobe of the liver is adherent to the diaphragm by strong fibrous bands in which are a number of large vessels. These latter penetrate the diaphragm and anastomose with vessels in a mass of pleural adhesions. The spleen is firmly adherent to the diaphragm and to the stomach. These adhesions are dense and in some places calcified. The stomach is small, extending only a short distance below the costal margin. The parietal peritoneum is considerably thickened and shows numerous dilated vessels. Otherwise the abdomen and pelvic viscera are normally disposed.

Thorax: The ribs are brittle, with thin walls, large spaces and little marrow. The pleural cavities are almost obliterated by rather old fibrous adhesions which are easily separated. There is no excess of fluid. The pericardial sac is normal.

Heart: Weight 270 gms. Presents nothing of note.

Lungs: In addition to the pleuritic adhesions above noted, the principal point of interest is the marked sclerosis of the pulmonary vessels which involves not only the large trunks, but even the smaller vessels which stand out conspicuously on section.

Spleen: Shows a thickening of the fibrous trabeculæ and marked general sclerosis of the vessels.

Stomach: Is contracted; the pylorus is thickened and resembles the external os of the uterus. On opening the stomach along the greater curvature a remarkable condition is disclosed (Fig. 2). The surface is covered with a blood-stained mucous exudate and is everywhere studded with polypus-like masses of varying size. The mucosa, as a whole, is of a deep red color except along the upper portion of the lesser curvature. The discoloration is intensified in the mucosa covering the polypi. These polypi vary greatly in appearance, showing every gradation from small sessile masses 0.5 cm. in diameter to those having a definite stalk and a cauliflower-like extremity, some of which have a diameter of 2 to 3 cm. Some of the largest nodules show no pedicle. Such a group is found in a circular arrangement near the cardiac orifice. The periphery of this circle is composed of several nodules which are in intimate contact. In the center is a crater-like depression which is covered by an unbroken mucosa. The extreme diameter of the mass is about 6 cm., height 2 cm., and the diameter of the crater about 3 cm. Section through the polypus-like masses shows them to be for the most part quite superficial, only involving the mucosa and submucosa. The cut surface of these is reddish, mottled by small translucent cysts and grayish white, more opaque areas. In several nodules, especially those above described in the region of the cardia, this grayish-white tissue composes the entire polyp. In two of these the underlying muscularis is thickened and firmer in consistence, with translucent or colloid strands invading and separating the muscle bundles; this involvement of the muscularis extends only about 2.5 cm. beyond the bases of these polypi.

Intestines: The peritoneal surface of the intestine is not uniform, but thickened here and there by small milky patches. Many small nodules may be felt in the wall of the gut. On opening the intestine along the mesenteric border the mucosa is everywhere covered with blood-stained exudate. The rugæ are prominent and somewhat œdematous. The entire intestinal wall is beaded with nodules. Some project slightly and are covered by a darker red mucosa. On transillumination it is seen that these nodules are innumerable and occasionally

[1] In order to study the relation of the nodules to the blood-vessels, an injection of Berlin-Blue was begun within twenty minutes after death. Fluid was forced into the left brachial artery under 200 mm. Hg. pressure, the excess being allowed to drain from the cephalic vein. The injection continued for two hours.

arranged in chains following the long axis of the bowel. In many places they are confluent. They are seen to lie at different levels in the intestinal wall, some, as above described, just beneath the mucosa, others near the peritoneal coat, showing through as pale brownish spots. About these latter small vessels radiate in the peritoneum. The individual nodules vary from 2 to 6 cm. in diameter. On section these nodules are sharply defined, rather firm in consistence, and have a pinkish-brown color. It is of interest to note the presence of these nodules in the œsophagus, duodenum, throughout the small and large intestine, and as subsequently shown on histological examination, also in the stomach.

There were no gross abnormalities in the mesentery.

Liver: Measures 21 x 15 x 9 cm. and weighs 1070 gms. The surface of the liver is very irregular and nodular. The capsule is delicate except at the point of origin of the vascular adhesions above described. The vessels in these fibrous bands have extremely thick sclerotic walls. The liver is firmer than normal. On section the normal architecture is absolutely obliterated and coarse bands of fibrous tissue divide the liver into false lobules of varying size. Small areas of semi-translucent, brownish liver tissue are seen throughout, while most of the tissue between the fibrous bands is yellow and opaque. Here and there small islands of regenerating liver tissue project from the cut surface. These are circumscribed, pale brownish in color, and not involved by the fibrous overgrowth.

Pancreas, Adrenal, Pelvic Organs: Present nothing noteworthy.

Kidneys: The blood-vessels are everywhere prominent as a result of a thickening of their walls. There is also a slight increase in connective tissue.

Blood-Vessels: The aorta shows extreme sclerosis, and chronic processes are seen with atheromatous ulcers and calcified placques lying side by side. There is a diffuse dilatation of the arch and a large thrombus overlies its descending portion. The veins also show an extreme grade of sclerosis.

Microscopic Notes.

Subcutaneous Nodules: Skin nodule No. 1 removed during life (Dec. 24, 1908). The section includes the skin and subcutaneous tissues. Lying beneath the skin is a small nodule which is composed of large cavernous sinuses containing well-preserved red blood. The walls of these sinuses are, for the most part, quite thin, lined on either side by flat endothelial cells, and containing between these a pinkish staining ground substance in which an occasional spindle nucleus is to be made out. Toward the periphery of the nodule the walls become slightly thicker and more cellular, resembling fibrous tissue.

Skin nodule No. 2, removed during life (Aug. 15, 1909). This nodule was cut in serial sections to show its relation to the vessels. The sections show an overlying layer of skin which is uninvolved by the tumor mass, and lying in the subcutaneous fat is a small nodule which is quite cellular. It is composed of many spindle cells which, on tangential section, have long nuclei with pointed ends. These show an outer nuclear membrane and pale protoplasm, in which numerous darker staining chromatin granules are found. The outline of the cells is, for the most part, made out with difficulty, but where they are seen, they are found to be relatively short; their protoplasm staining pale pink with delicate prolongations. The blood spaces described in Section 1 are very much less conspicuous in this section, although the tumor is quite vascular. The walls of the spaces, however, do not correspond in any way to those described in Section 1; for they are made of spindle cells similar to those described in the body of the tumor. One sees, in studying the series, that, although numerous small vessels can be seen to enter the nodule in its course, there is no large vessel connected with the tumor at any part. At no place does the mass seem to be connected with nervous tissue. An occasional nerve is found in the subcutaneous tissue, but none of these are in contact with the tumor, nor can any be seen projecting into the mass. The nodule varies somewhat in its consistence; for the most part, it is quite firm, composed of the spindle cells, above described, but occasionally small, irregular endothelial lined cavities are to be made out.

Skin Nodules at Autopsy: In order to study the nature of these vascular spaces to a greater advantage, the brachial artery was exposed and Berlin-Blue was injected. Several nodules were removed from the injected limb and studied in serial sections. In all, about 25 nodules were examined. Suffice it to say that they are all quite vascular, and in many of them there are hæmangiomatous caverns. In the surrounding subcutaneous tissue many vessels are to be found, but only small ones seem to be in direct contact with the tumor. The larger ones show an interesting change which will be described below.

On detailed examination, the nodules are, in general, quite similar. They vary somewhat in their characteristics, and it will suffice to describe completely one in which a composite picture is found, practically including the variations.

One sees a tumor mass (Fig. 3) surrounded partially by a definite membrane which is composed apparently of muscle. The cells are long and spindle-shaped, with long, pale staining nuclei, in which a considerable chromatin network can be seen. The protoplasm of these capsule cells is pale pink and stands out in sharp contrast to the cells of the tumor which have much less protoplasm and more deeply staining nuclei. This capsule surrounds the tumor in part only. In other parts it has greatly thinned out and allows the tumor mass to project into the subcutaneous fat. The tumor varies somewhat in its consistence; while in one area it is quite cellular and only a small number of blood-vessels can be made out, in other areas it is composed of blood spaces separated from each other by thin walls lined with endothelium (Figs. 4, 5).

The spaces are irregular, gradually becoming smaller as they project into the more cellular tumor. As the spaces grow smaller, their walls become considerably thickened. The walls of the large spaces are, in places, composed of but a single layer of endothelium, or may show a double layer, one lining each adjacent cavity (Fig. 6). Between this layer of endothelial cells there is a small amount of pink, homogeneous

tissue in which an occasional slender, deep blue-staining nucleus occurs. The blood in these spaces is well preserved, normal blood. As above stated, there is a simultaneous increase in the thickness of the walls with a decrease in the size of the spaces. The walls increase by fusion and by proliferation, and lose their fibrous character and become cellular. These cells resemble in every respect those lining the cavities. In this manner the angiomatous portion of the tumor merges on all sides into the cellular mass above described.

It is to be noted, however, that some of the nodules, even small ones, are composed of cell masses without blood spaces. This was brought out very characteristically in the study of one nodule in serial section, which had an hour-glass shape. This hour-glass had for its center a thick-walled blood-vessel. From the center the wall was distended and thinned toward the poles by the tumor mass, and in places the mass protruded through into the surrounding tissue. The lumen of this vessel was filled with cells indistinguishable from the endothelial lining and similar in all respects to those making up the tumor mass (Fig. 7). The appearance of this nodule led to a detailed study of the blood-vessels.

The Blood-Vessels: There was evident a marked increase in number of the vessels throughout the connective tissue, and these vessels showed great thickening of their walls, which involved all three coats. The large vessels show several types of thickening and diminution of their lumen. The changes are most marked and varied in the intima and subintimal tissue.

From a simple oval slit-like lumen (Fig. 8), lined by one layer of cells and surrounded by a greatly increased subintimal layer, poor in nuclei, it is possible to trace by steps, a gradually increasing complexity in the form of the lumen. In some vessels the lumen is encroached upon by nodular projections which give it an irregular outline like that of the Fallopian tube. In still others, bridges of tissue extend across the lumen, dividing it into separate channels (Fig. 9). These strands may be lengthened and folded so as to give the lumen a labyrinthine appearance. The bridges are lined by a single layer of endothelium and made up of the thick subintimal coat.

The small vessels are likewise greatly increased in number, many of them showing a marked thickening of their walls. While some of these show an increase in all their coats, the changes are, for the most part, in the endothelial lining. The endothelium may be increased uniformly to several layers, or it may proliferate in a nodular manner, and project into the lumen like a polyp (Fig. 10).

In other vessels the masses of endothelium seemed to lie free in the lumen and no connection with the wall could be made out in serial sections.

In another group of vessels the endothelium forms nodal thickenings of several layers at different points on the wall. Finger-like columns of cells project into the lumen from these nodes and at times the space between the fingers is bridged by a single cell. In this way the lumen is divided into two or more parts, forming angiomata (Figs. 11, 12, 13, 14).

In still other vessels multiple caverns are formed in a different manner. Here the endothelium seems to dip into the wall, or even to push the wall before it into the surrounding tissue, as bays push in from the borders of a lake. The necks of these bays are narrow and may be closed by a mass of endothelium, when we have separate caverns in juxtaposition (Figs. 15, 16).

This is a definite new formation of blood-vessels by budding similar to that seen in granulation tissue and in the embryo.

In correlating the foregoing detailed studies, we see first, a striking generalized sclerosis of the arteries and veins, corresponding to that described in the subcutaneous vessels. This thickening may be seen in all the coats, leaving a slit-like lumen, or there may be an irregular proliferation of the intimal tissue in nodes, or strands, which divide the lumen into narrow channels, or obliterate it altogether.

Associated with this narrowing of the larger stream bed, there is a development of many small vessels. But here again many of the small vessels show marked thickening and, in some, the changes are confined to the endothelium alone.

This endothelial over-growth is expressed in different modes. The simplest type is found in a loop-like dipping of the endothelium into the surrounding tissue. The loop may then be cut off in its narrow part, leaving a separate cavity.

Again, nodal proliferation may take place at several points, on the wall and these nodes may be prolonged to form bridges dividing the vessel into different compartments.

Lastly, the nodal proliferation may fill the vessel with a solid mass of cells and even invade the surrounding tissue.

In this way we trace the formation of cavernous angiomata and of solid tumors to the same basal process, namely, the vegetative overgrowth of endothelium. In comparing the larger nodules of the subcutaneous tissue, we find a close relation to the changes described in the small vessels, some of these nodules showing cavernous structures in which the endothelium has obliterated the cavities in varying degrees; and in others, solid masses of endothelial cells without any trace of a preceding angioma. The question arises whether these nodules are all primary or in part metastatic. From the observations above described—that isolated masses of endothelial cells occur in some of the smaller vessels, and that no root or connection with the neighboring wall could be found in serial section, it seems probable that metastases play some part in the multiple tumor formation.

Intestinal Nodules: These all arise in the submucosa. They vary considerably in size; the smaller ones do not invade either the mucosa or the muscularis, but as they grow larger these structures are gradually involved. The tumor mass in some places pushes the mucosa outward and is separated from it by the muscularis. In other areas this line of demarcation is not apparent (Fig. 17), and one sees the tumor invading directly the villi. Such villi no longer show their normal structure; they are dilated and club-shaped, entirely denuded of their surface epithelium, and show only an occasional small atrophic gland in their bodies. The villus, except where it is replaced by tumor cells, is composed of dilated blood-vessels

and areas of round cell infiltration. As the tumor invades the muscular coat it follows the course of the vessels in finger-like projections which gradually obliterate the muscle bundles (Fig. 18).

The nodules vary considerably in structure. Some are quite solid, others contain numbers of well-formed blood-vessels (Fig. 19), and others again show large irregular cavities lined with endothelium (Fig. 20). These cavities do not contain blood, but only precipitated albuminous material. The nature of the above cavities is best shown in the portion of intestine injected at autopsy. This part of the gut was first injected through the mesenteric artery with carmin-gelatin, and then the lymphatics of the same piece were injected with India ink. The India ink injection was not altogether successful, but did enter some of the nodules.

On serial section of the injected nodules, their general charactertistics are as described above. The carmin-gelatin has filled all the blood-vessels in the several intestinal coats and in the tumor nodules. Even the finest capillaries are injected. It becomes apparent at once that many of the large vessels and spaces with endothelial lining contain neither blood nor injection mass, but only the albuminous material previously noted (Fig. 20). These cavities lie within the tumor nodules and resemble exactly those described in the subcutaneous tissue, except that they do not contain blood. The cavities are divided into compartments by strands of tissue, varying in thickness. The thinner strands consist of two layers of endothelial cells with a very slight fibrous tissue between. In the thicker ones the walls are made up of numerous layers of endothelial cells similar to those lining the cavities. The endothelial cells are spindle-shaped, with long blue-staining nuclei and scanty pink protoplasm. Here and there the nuclei are more vesicular or show mitoses.

Selecting a node which has been injected with India ink, as well as carmin, we find that the cavernous spaces are filled with the black mass (Fig. 21), and on tracing this through a series of sections, it is found that one of the large injected lymph vessels of the submucosa opens directly into the cavity. It is, therefore, certain that the angiomata of the intestine arise from the lymphatic vessels. That they are not hæmangiomata is evident from the fact that they do not contain any of the carmin-gelatin, which fills all the blood-vessels, but only the India ink, which is confined to the lymphatic channels.

The cavernous areas merge on all sides into solid tumors, just as the areas described in the hæmangiomata from the subcutaneous tissue.

Scattered through the more solid parts of the nodules are narrow channels lined by endothelium. These do not contain blood or carmin-gelatin and are evidently not blood-vessels. On tracing them through serial sections, they gradually increase in size and merge into cavernous spaces, or into large lymphatic vessels (Fig. 22). These latter show large projections into the lumen from either wall, which are apparently valves. These lymphatic channels are especially numerous about the larger blood-vessels which intersect the tumor nodules.

The blood-vessels themselves show a general thickening of their walls. Here and there the endothelium of the lymphatic channels is proliferated to form nodes on the vessel wall, projecting into the lymph spaces. The cells in the nodes have the characteristic perithelial arrangement, with the strands of cells at right angles to the axis of the vessel (Fig. 23). In many instances this nodular growth completely surrounds the blood-vessel.

In résumé, then, we find that the endothelium of the intestinal lymphatics has proliferated at many points to form nodular tumors. In these tumors many of the lymphatic vessels are obliterated by the endothelial masses. Other vessels are dilated, and here and there the proliferation has resulted in definite cavernous angiomata.[1]

The structural similarity of the subcutaneous and intestinal tumors suggests a possible analogy in their mode of formation. In the subcutaneous tissue there is a marked obliteration of the larger blood-vessels (generalized sclerosis) and an active production of new blood-vessels has taken place. In these small vessels the endothelium shows marked proliferative growth leading to the formation of angiomatous caverns and to solid endothelial tumors. Similarly, from some cause unknown, there has been an active proliferation of the endothelium in the intestinal lymphatics, leading, again, to the production of cavernous angiomata and solid endothelial tumors.

Stomach.

A. Mucosa in General: The gastric mucosa (Fig. 24) is thinner than normal and is everywhere covered by an exudate composed of mucus, red blood cells, and desquamated epithelial cells. The mucosa presents a picture of diffuse chronic gastritis with increase of fibrous tissue and round cell infiltration. In many places the villi are denuded of epithelium, but, as the submucosa is approached, the glandular structures become more prominent and show many changes. Some glands are atrophic, with degenerated epithelium. Others are hypertrophied and show as tortuous crypts or as groups of normal gland tissue in cross-section.

The glands may become greatly dilated at their bases and be lined either by columnar mucous cells or by a flat epithelium.

B. Polypi: These are so numerous and show such complex changes that we shall only describe the types of variation observed.

The simplest polypi are sessile and show a mass of acini separated by a small amount of fibrous tissue (Fig. 25). Many of the acini are slightly tortuous and all are lined by normal goblet cells (Fig. 26).

All the other types of polypi show not only glandular hypertrophy, but also chronic inflammatory changes. In some of them the inflammatory change predominates and there are

[1] Tumors of similar structure were found in the œsophagus, stomach, mesentery, and adrenal capsule, as well as in the intestines.

FIG. 1.—Drawing of right fore-arm showing subcutaneous nodules.

FIG. 2.—Photograph of stomach opened along the greater curvature.

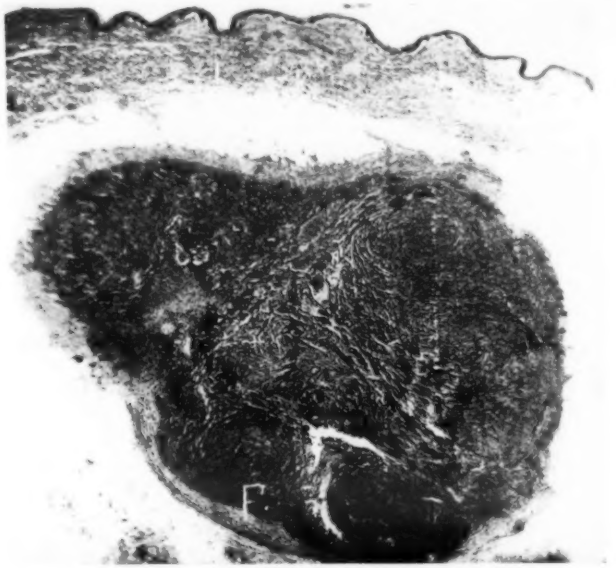

FIG. 3.—Subcutaneous nodule of mixed type with angiomatous and solid portions.

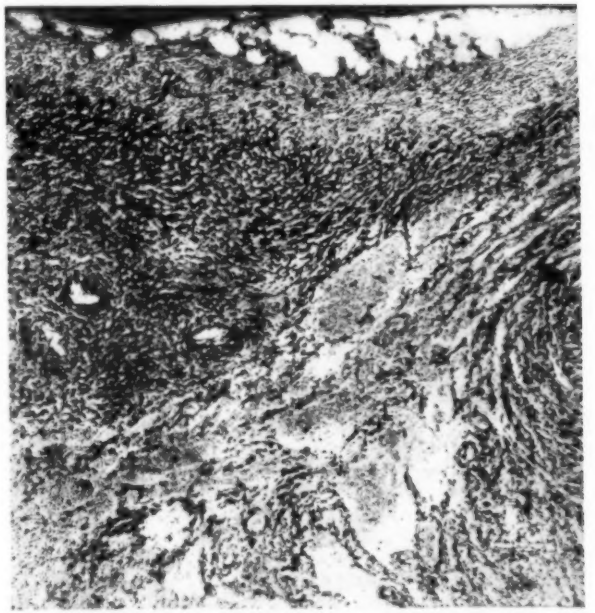

FIG. 4.—Same as Fig. 3. Higher magnification showing capsule and blood spaces.

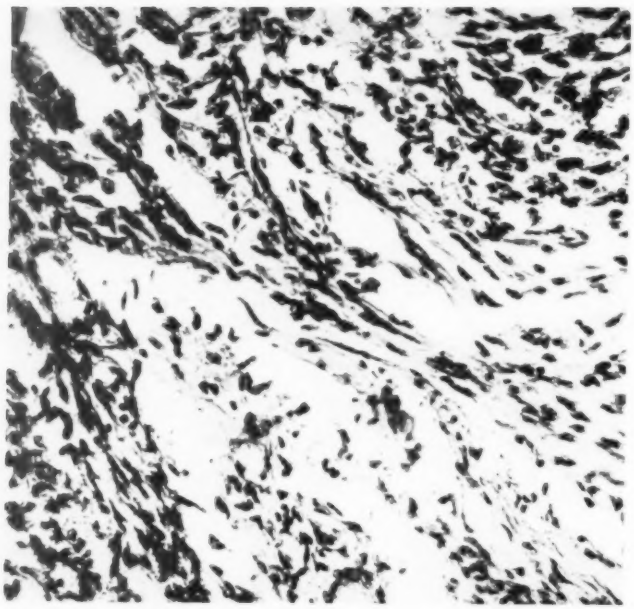

FIG. 5.—Same as Fig. 3. Higher magnification showing character of endothelial cells.

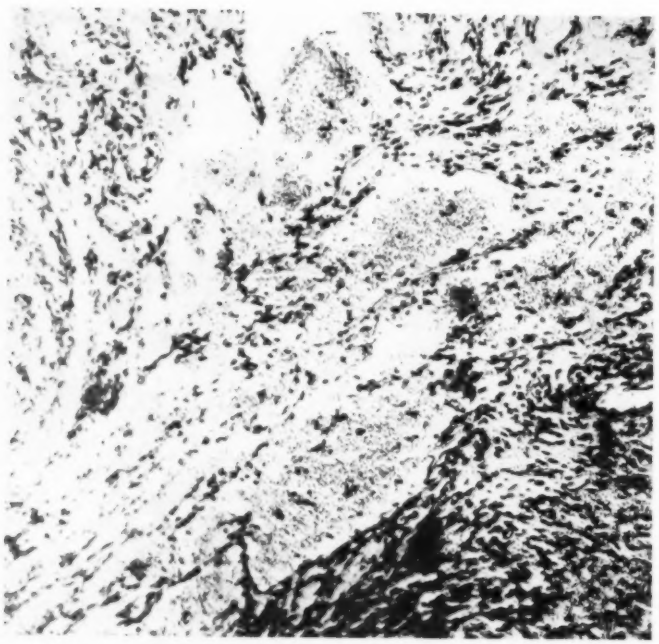

FIG. 6.—Same as Fig. 3. Higher magnification showing character of angiomatous portion.

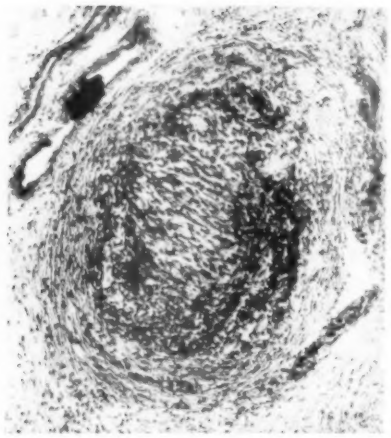

FIG. 7.—Center of hour-glass nodule. The lumen of the vessel is completely filled with endothelial cells.

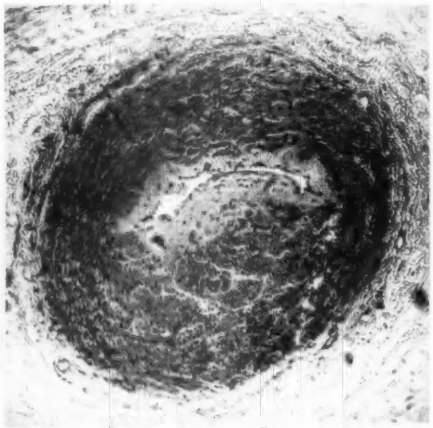

FIG. 8.—Sclerotic subcutaneous vessel showing slit-like lumen.

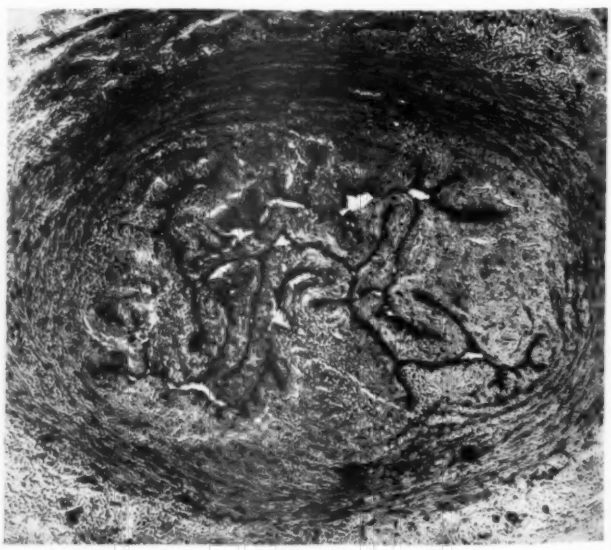

FIG. 9.—Another vessel showing extreme proliferation of intimal and subintimal coats with labyrinthine lumen.

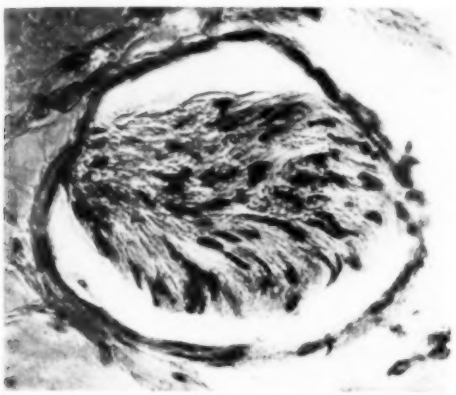

FIG. 10.—Polypus-like outgrowth of endothelial lining of a small vessel.

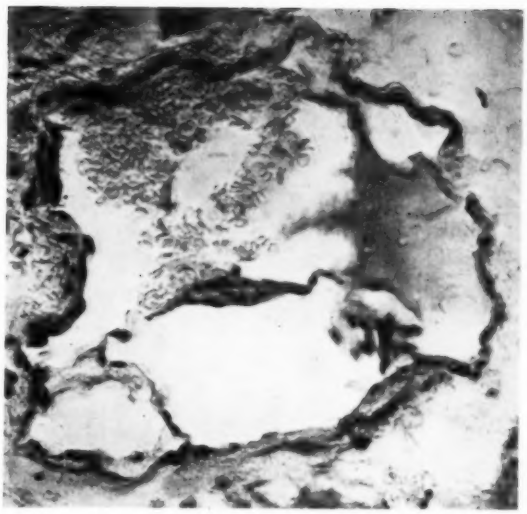

FIG. 13.—Subdivision of larger vessel by strands of endothelium.

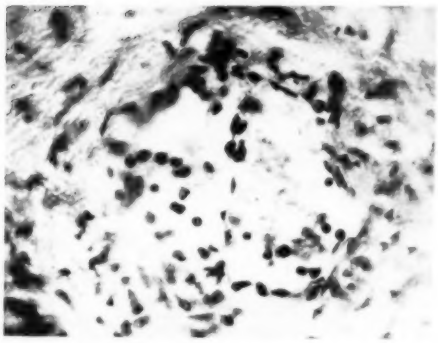

FIG. 11.—Outgrowth of endothelial strands in small vessel forming separate channels.

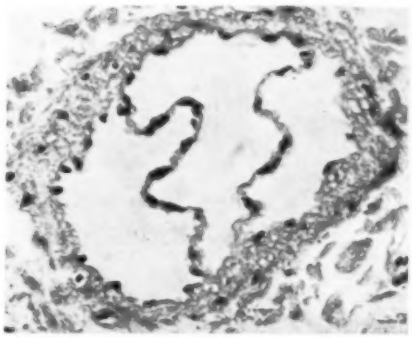

FIG. 14.—Valve-like strands in small vessels.

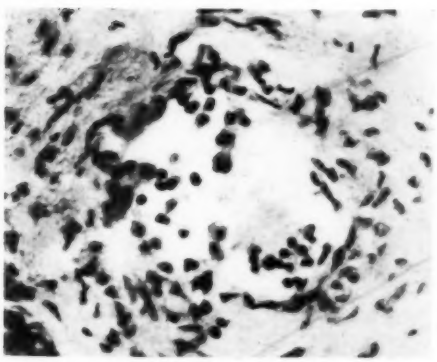

FIG. 12.—Same as Fig. 11. Slightly different focus.

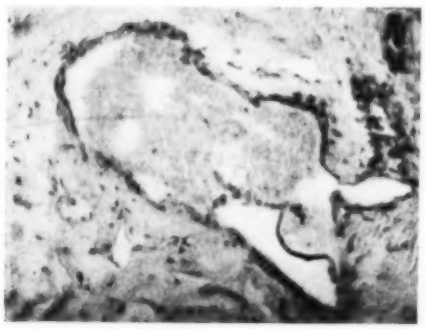

FIG. 15.—Formation of separate channels by budding.

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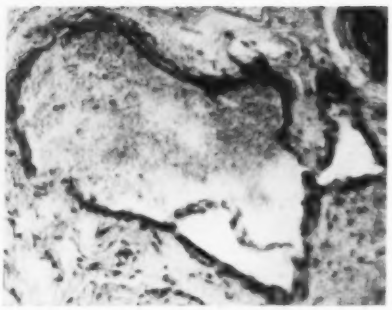

FIG. 16.—Same as Fig. 15.

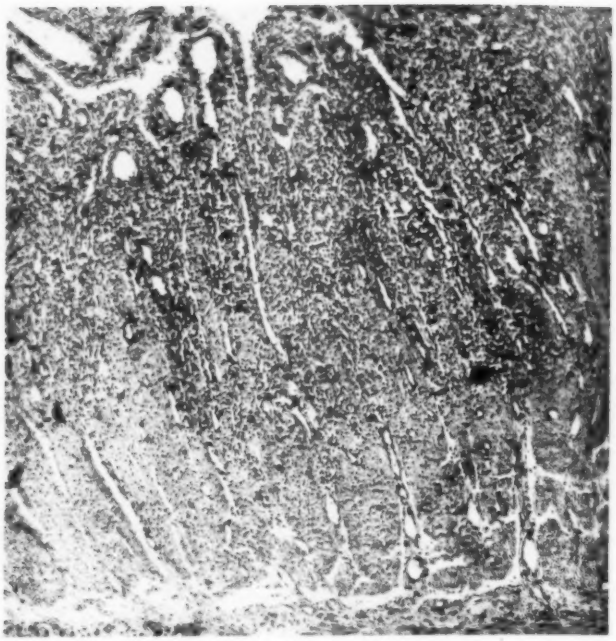

FIG. 18.—Intestinal nodule invading muscularis.

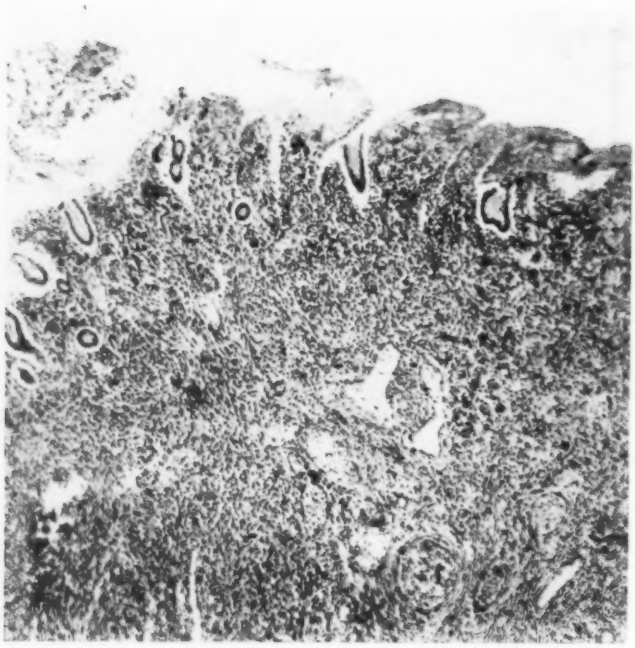

FIG. 17.—Intestinal nodule invading villi.

FIG. 19.—Intestinal nodule showing larger blood-vessels.

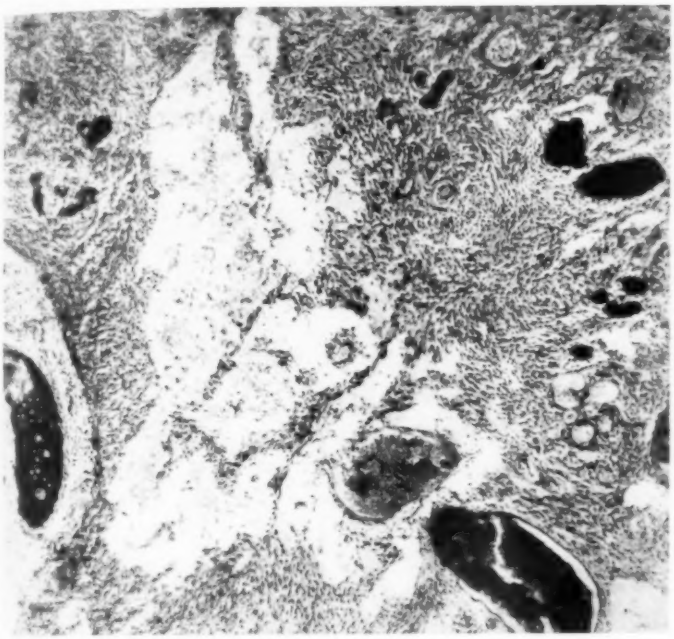

FIG. 20.—Intestinal nodule showing lymphangiomatous caverns.

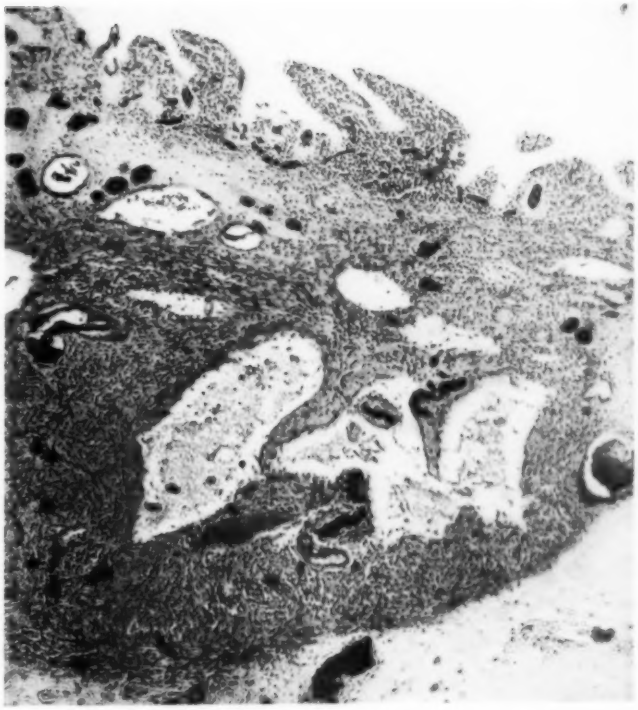

FIG. 22.—Intestinal nodule showing dilated lymphatics with valves.

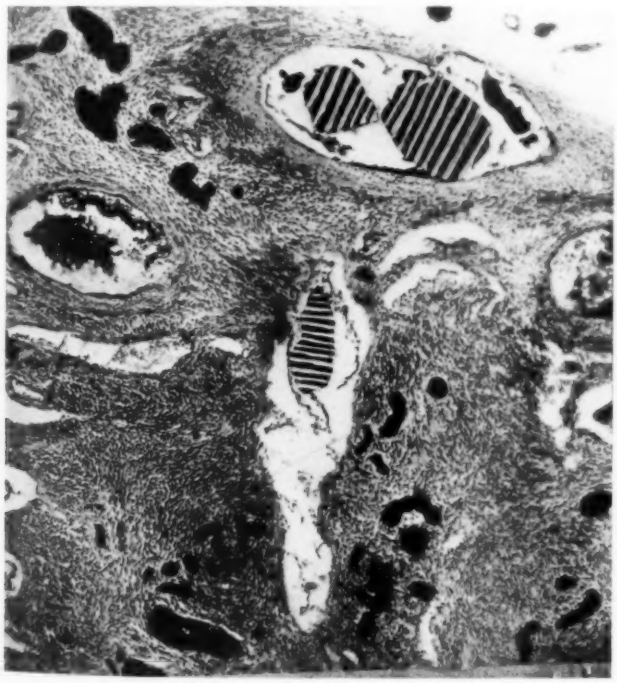

FIG. 21.—Intestinal nodule injected with India ink. White lines crossing the black show injection mass. Dark masses without lines show carmin-gelatin in the blood-vessels.

FIG. 23.—Same as Fig. 19. Higher magnification showing endothelial proliferation in the lymph spaces.

UofM

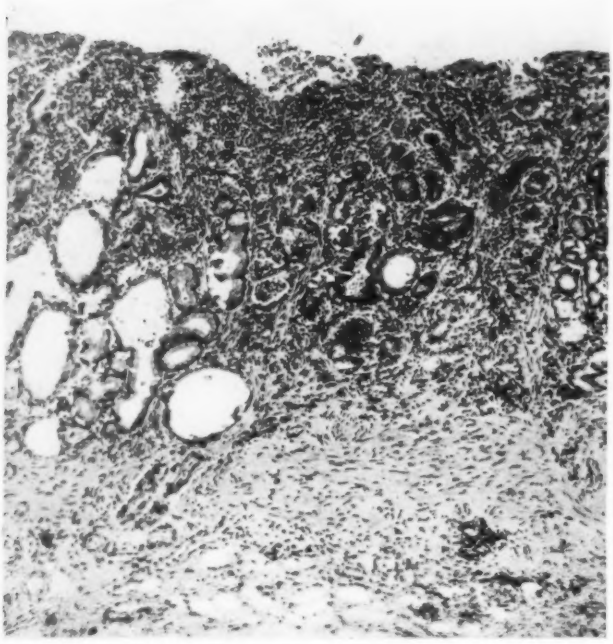

FIG. 24.—Chronic gastritis.

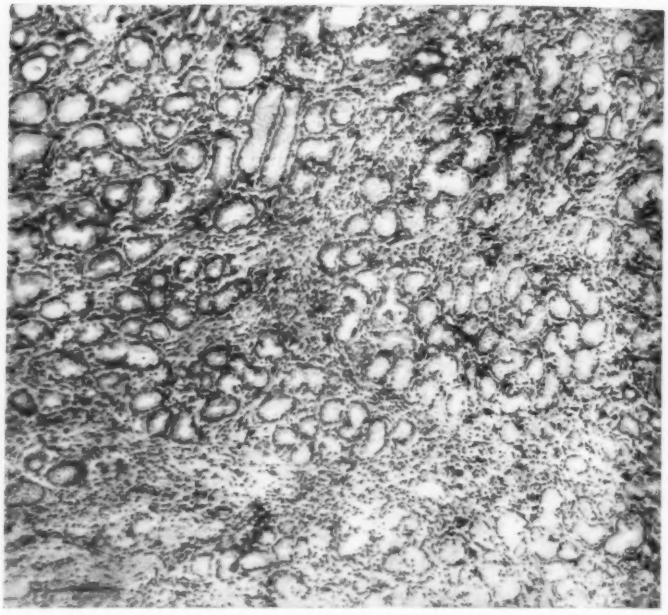

FIG. 26.—Same as Fig. 25. Higher magnification.

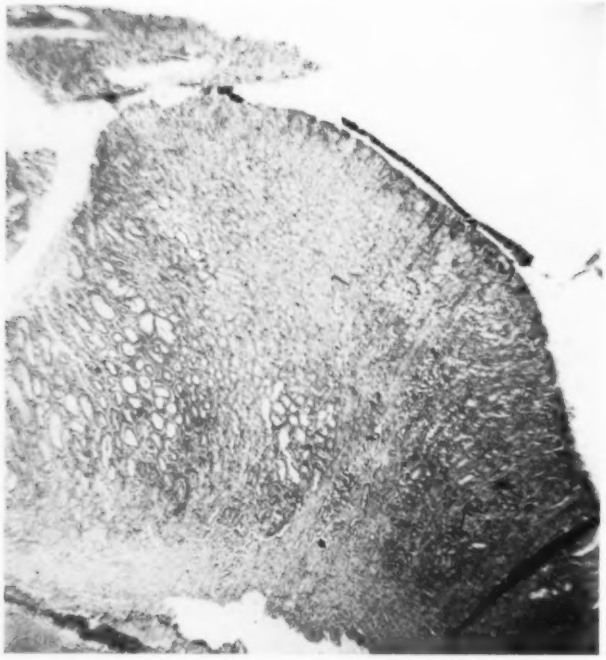

FIG. 25.—Sessile polypus.

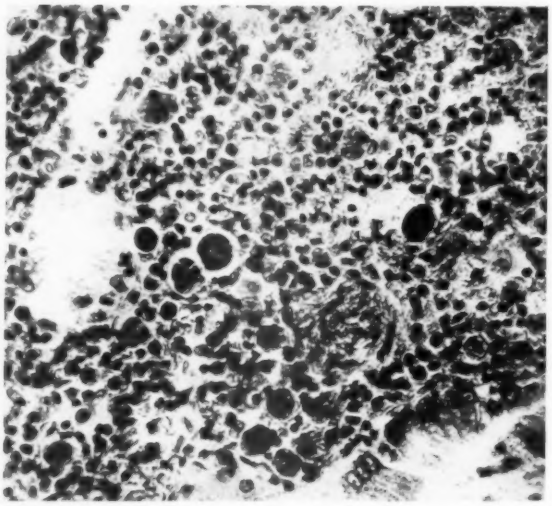

FIG. 27.—Chronic gastritis showing "Russell's Bodies."

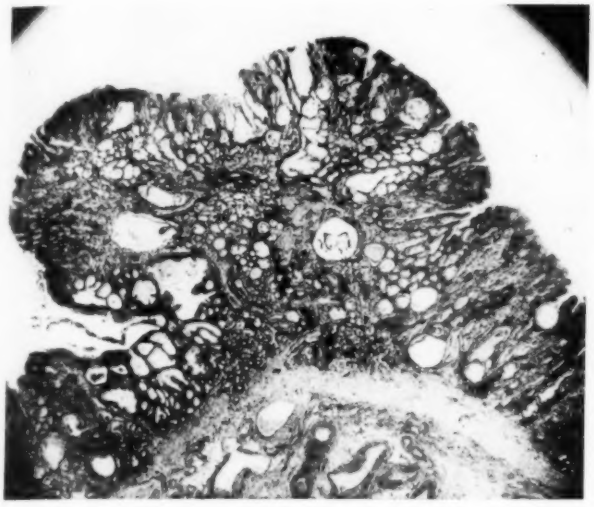

FIG. 28.—Cauliflower polypus.

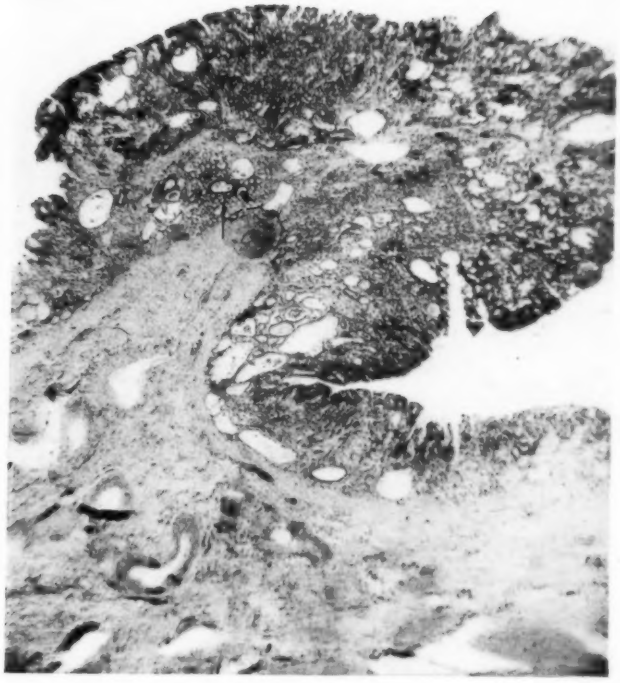

FIG. 29.—Cauliflower polypus.

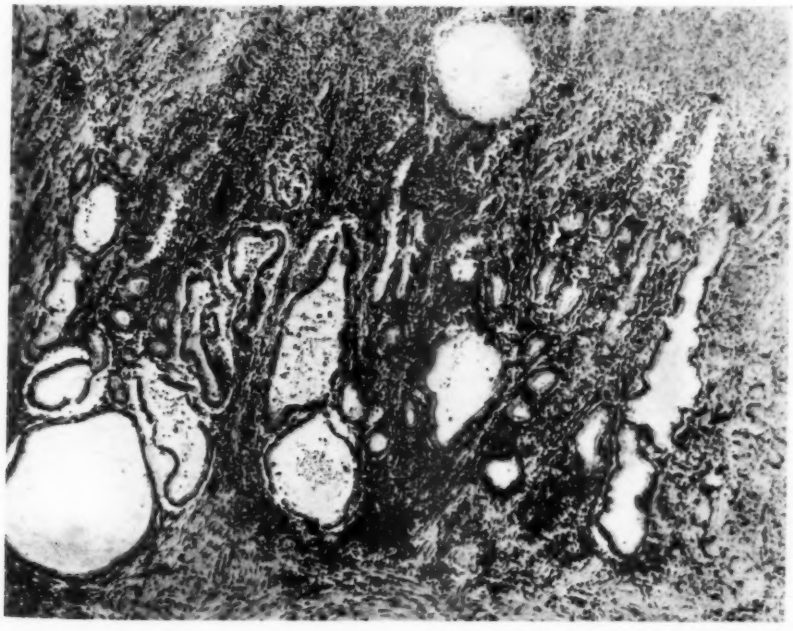

FIG. 30.—Same as Fig. 28. High magnification showing tortuous and dilated acini.

FIG. 31.—Same as Fig. 29. Higher magnification of acinus, showing papillomatous proliferation of epithelium.

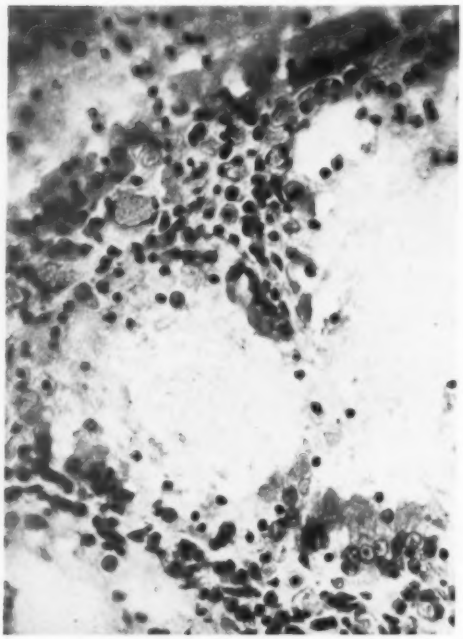

FIG. 32.—Same as Fig. 31. Higher magnification showing atypical epithelial cells.

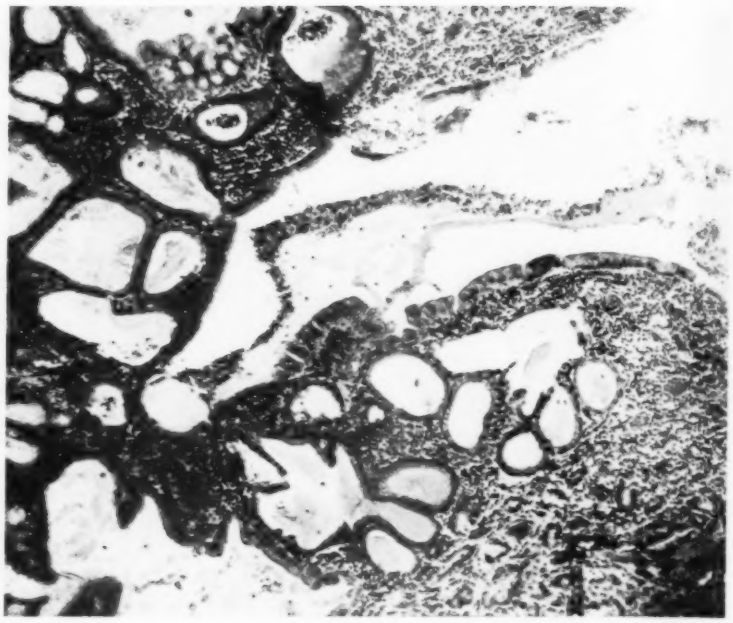

FIG. 33.—Crypt from Fig. 28.

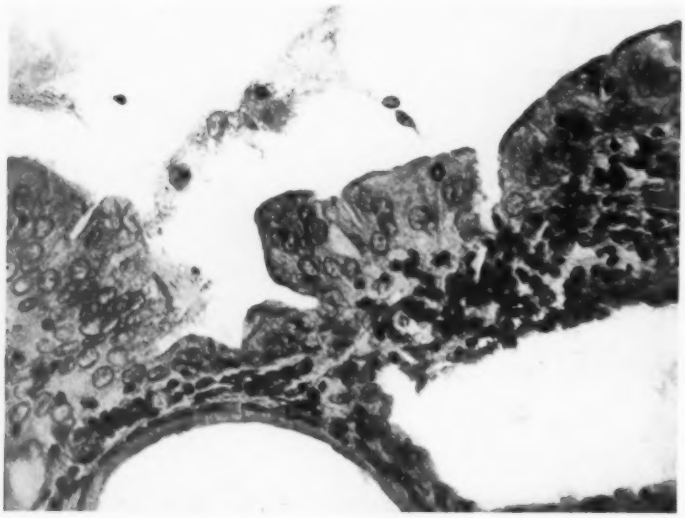

FIG. 34.—Same as Fig. 33. Higher magnification showing proliferation of epithelium and multinuclear cells.

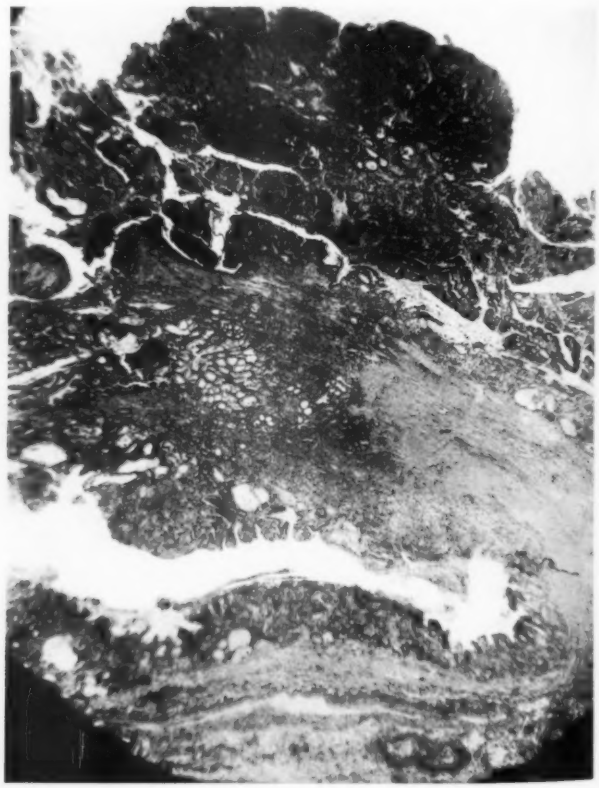

FIG. 35.—Cauliflower polypus showing adenomatous change.

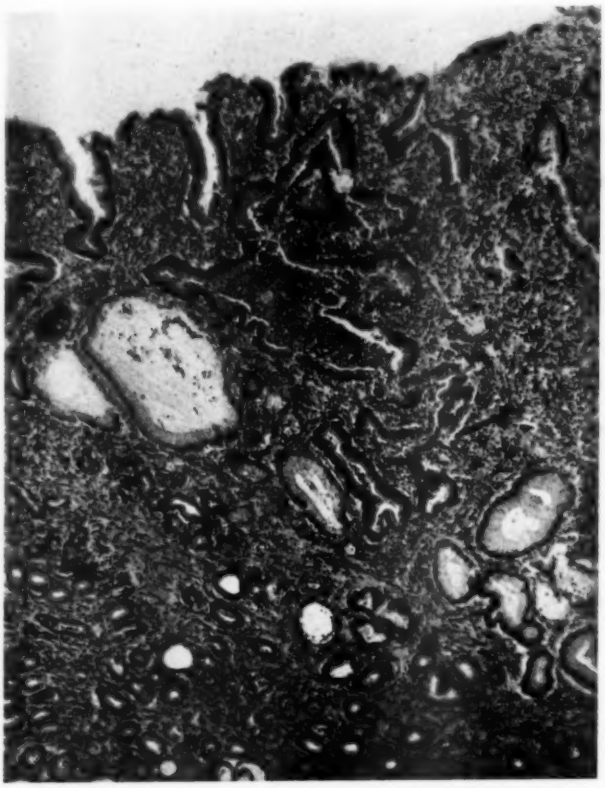

FIG. 36.—Same as Fig. 35. Higher magnification.

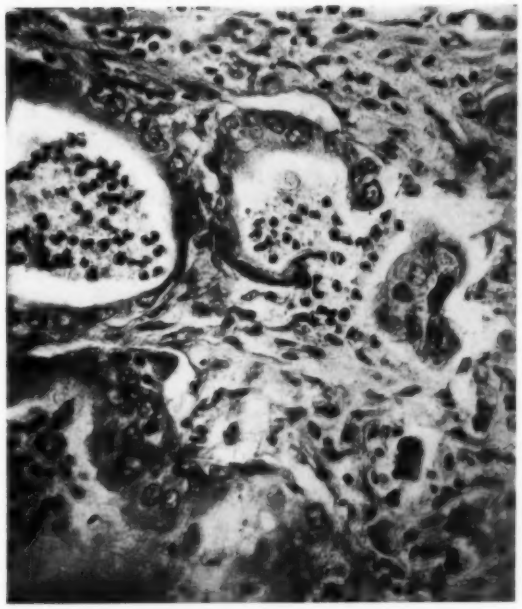

FIG. 38.—Acinar epithelium invading basement membrane.

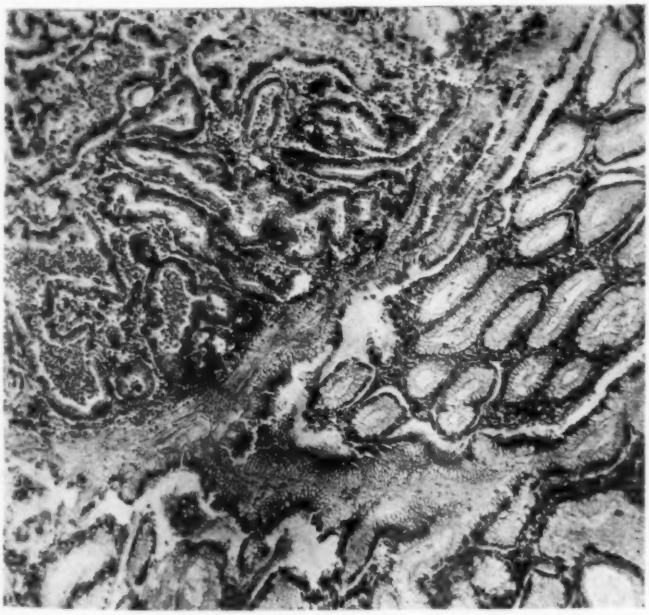

FIG. 37.—Portion of adenomatous polypus showing normal and undifferentiated acinar epithelium.

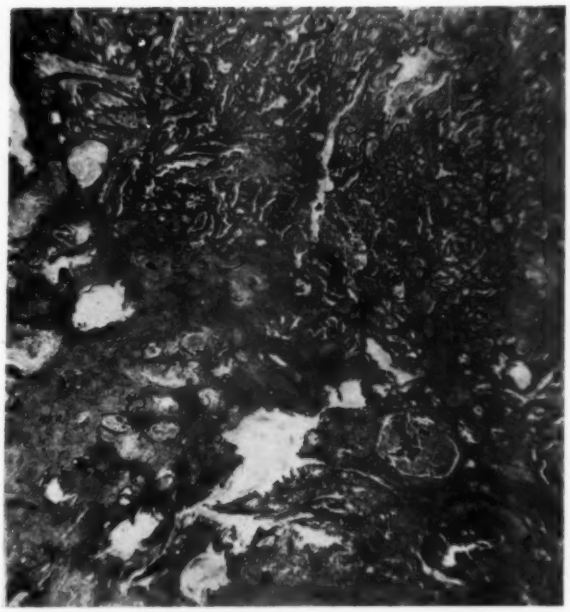

FIG. 39.—Cancerous polypus invading muscularis.

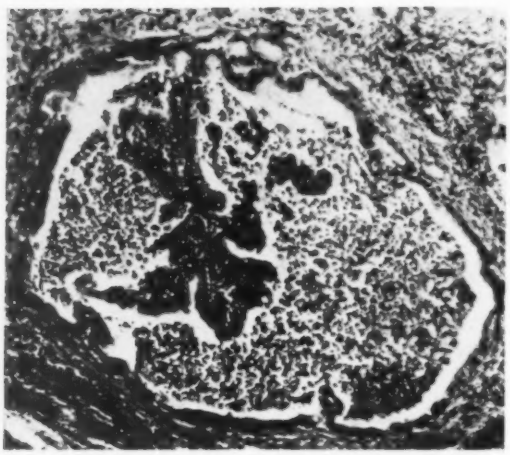

FIG. 40.—Same as Fig. 39. Higher magnification of acinus.

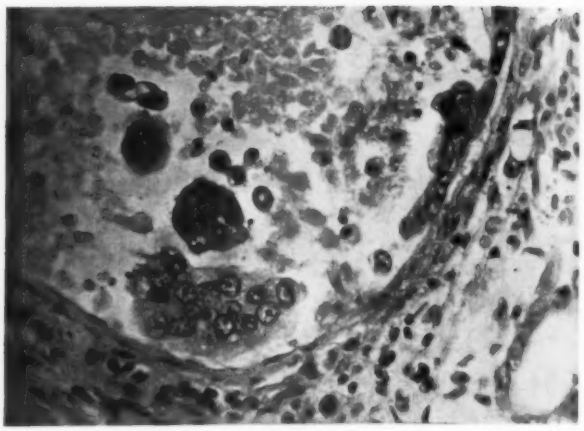

FIG. 42.—Same as Fig. 41.

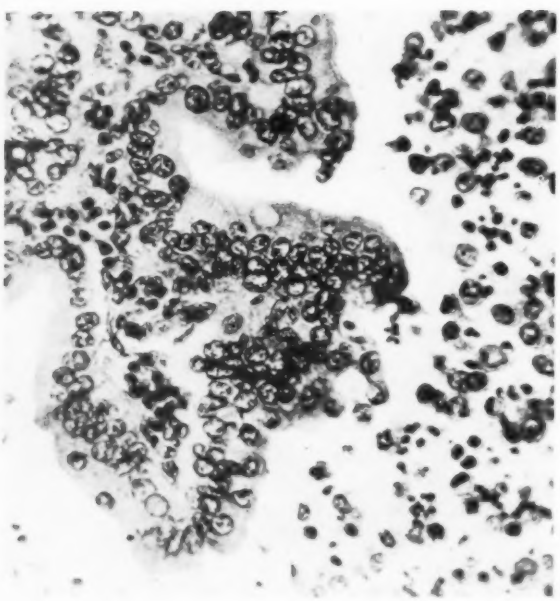

FIG. 41.—Same as Fig. 40. Higher magnification showing cancerous character of epithelium.

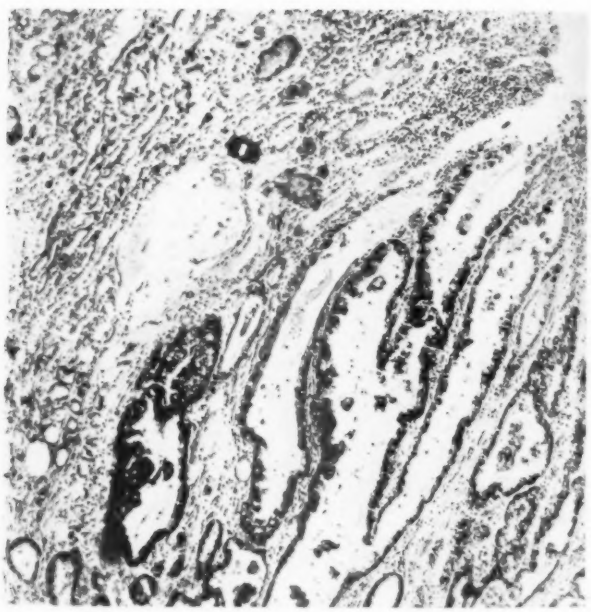

FIG. 43.—Cancerous metamorphosis of mucosa uninvolved by polypus.

large areas where no acini are found, but only masses of fibrous tissue with round cell infiltration. Many cells in these areas show a hyaline, pink-stained protoplasm, and rather flattened dark blue nuclei. Some of these cells show the hyaline portion divided in small round masses about the size of a red blood cell, and the nuclear material as pale blue spots. In others the cell membrane has disappeared and the round particles are scattered in the interstitial tissue (Fig. 27).

In the next group of polypi the hypertrophy is modified by the inflammatory process and is varied more from normal structure (Figs. 28, 29). The acini are tortuous or dilated and may show normal mucous cells or flat epithelium (Fig. 30). In other areas the acini show an infolding of the epithelium which may form subdivisions of the acinus (Fig. 31). Here the epithelium may change from the normal goblet cell to a still longer cell with large central nucleus and granular protoplasm. Some of these nuclei are dividing (Fig. 32). Still other acini may be prolonged toward the base of the polyp. These show several layers of cells which have lost their secreting character and masses of protoplasm occur which have more than one nucleus (Figs. 33, 34).

In still another group of polypi the stalk is more prolonged and narrow, and covered by the inflamed mucosa (Fig. 35). At the cauliflower-like extremity, however, we see some chronic inflammation and simple hypertrophy, but by far the greater number of acini show the marked abnormalities described in single crypts of the foregoing group (Fig. 36). That is, the acini are irregular and tortuous, with large columnar epithelial cells of undifferentiated type.

A further abnormal development is seen in the next two types of polypi. These are sessile and composed wholly of convoluted glands. In the first of these there are some crypts with normal mucous cells. But most of the glands have high columnar epithelium with actively dividing nuclei (Fig. 37). At the base of the polyp, where the dilatation and epithelial growth are most marked, some strands of epithelial cells have penetrated the basement membrane into the adjacent tissue (Fig. 38).

In the second type all the crypts are lined by an actively proliferating epithelium. Toward the base of the polypus the acini dilate and the epithelium and basement membrane project as irregular masses into the lumen which is filled with mucus and cell débris. Where these cavities invade the muscularis they are often imperfect and broken on one side (Fig. 39). The nodules of epithelium on the basement membrane may project either toward or away from the lumen (Fig. 40). The epithelium is of a definite vegetative character. The protoplasm stains deep blue, and is divided irregularly, often containing two or more deep black, or vesicular nuclei (Figs. 41, 42).

Many other polypi were examined in which the above described changes occur in varying degree and association. And it is to be noted that there are areas in the mucosa showing cancerous metamorphosis without polypus formation (Fig. 43).

In brief, we find in the stomach extensive chronic gastritis with multiple polypus formation. In these polypi we find associated with the gastritis, simple hypertrophy, benign and malignant adenoma, and cancer, with extensive invasion from multiple points of origin.

General Summary and Conclusions.

This case presents many unique features and is of interest, not only as a remarkable example of multiple heterologous tumor formation, but also as a basis for some generalization on the origin of tumors.

After a fairly wide examination of the literature, we were unable to find any like instance of multiple subcutaneous hæmangio-endotheliomata. Nor did we discover any record of a similar lymphangio-endothelioma formation throughout the entire intestinal tract. Lastly, also, we were unable to find any instance in which so many diverse types of epithelial tumor formation occurred in one stomach. So that, so far as we know, each of the three groups of tumors, present in this one case, is unique in the extent and character of its occurrence. And that all three should have occurred in one individual is truly remarkable.

It is inevitable that such an extraordinary coincidence of multiple tumors of different type in one individual should lead to some speculation as to possible common factors in their origin. We shall suggest therefore some hypothetical explanation of the facts observed.

Turning our attention, first, to the general picture, we find in an old man, with a marked alcoholic history, extreme generalized sclerosis of arteries, veins, and parenchymatous tissues. In the blood-vascular system we find an extreme grade of sclerosis affecting the aorta and larger arteries throughout the body, and a very marked phlebo-sclerosis, as well. In the subcutaneous tissue this sclerosis has resulted in obliteration of much of the stream bed and a compensatory formation of new vessels. These new blood-vessels are formed by the proliferation of the endothelium, as in granulation tissue. But in many places the endothelium loses its power of organization with a resultant exuberance of endothelial growth into cavernous angiomata. By a still further loss of this organizing force, the vegetative function of the cell predominates and we have the formation of solid endothelial tumors. The solid tumors may, in turn, give rise to metastases.

In considering the proliferation of the lymphatic endothelium in the intestine, we have no obvious factor, like the generalized sclerosis of the blood-vessels. It may be suggested, however, that the extreme portal obstruction, associated with the cirrhosis of the liver and the proliferative peritonitis and ascites, may play a part somewhat analogous. It may further be suggested that portal obstruction leads to over-loading of the lymph channels and that, in the attempt to compensate for the extra load, proliferation and new formation of lymph vessels may take place. Here again a loss of organization may lead to the development of cavernous angiomata and of solid endothelial tumors.

The changes in the gastric mucosa offer some points analogous to those considered in the discussion of the formation of the endotheliomata.

We may suggest a sequence here somewhat as follows: Cell destruction as a result of chronic alcoholism. Chronic gastritis as a protective effort on the part of the tissue. Regeneration in excess with polypus formation. And lastly, as a result of loss of organization, lawless growth with the production of adenoma and carcinoma, at many points simultaneously.

While the foregoing studies throw a certain, and we think important, light on the origin and method of tumor formation, it is equally certain that other factors, as yet unknown, play an even more important part in the determination of lawless cell growth.

No attempt will be made to give the extensive literature on the occurrence of multiple tumors. This field, in general, has been covered recently by Woolley (Bost. Med. and Surg. J., 1903, cxlviii, 1), while Versé (Arbeiten aus den pathologischen Institut zu Leipsig, 1908) has discussed exhaustively their occurrence in the stomach.

N. B.—In conclusion we wish to thank Professors L. F. Barker and W. S. Thayer for permission to use the case, Professor W. H. Welch for his interest and encouragement, and Dr. H. M. Evans for assistance in the injection of the specimens.

A REVIEW OF THE RECENT ADVANCES IN OUR KNOWLEDGE OF TROPICAL DISEASES.*

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When your secretary invited me to address your society, I accepted his invitation at once because I wanted an excuse to come to Baltimore. The invitation was accepted although I had no new piece of work sufficiently important and sufficiently interesting to you to furnish a subject for an evening's address; but I made up my mind to kill two birds with one stone and to bring my reading up to date by compiling from the literature an account of the most important advances which have been made in tropical medicine during the past year. It was hoped that it might be possible to entertain you for an hour by such an account.

It is quite unnecessary to remind you of the enormous amount of work which has been done during the past ten years, and still is being done, by workers in all parts of the world to elucidate the causation of tropical diseases. It is apparent to anyone who reads the ordinary medical journals that an enormous number of papers are published on subjects connected with tropical medicine. It is not so long since Rüge complained that it was quite impossible for one man to keep himself quite up to date in the literature of malaria alone; he may have exaggerated, but it certainly is almost impossible now for one man to read all that is written on tropical medicine and on the protozoa which cause so many of the diseases peculiar to warm climates. The number of papers on these subjects which appear in publications devoted to medicine in general—such as the *Lancet*, the *British Medical Journal*, the *Journal of the American Medical Association*, the *Deutsche medizinische Wochenschrift*, and so on—is not small; many more papers appear in the pathological journals —such as the *Centralblatt für Bakteriologie und Infektionskrankheiten*, the publications of the *Kaiserliches Gesundheitsamt* and the American laboratory journals; in addition to these there are a number of periodicals which are devoted solely to tropical medicine; they are, the *Journal of Tropical Medicine and Hygiene*, the *Annals of Tropical Medicine and Parasitology*, and the *Archiv für Schiffs- u. Tropenhygiene;* the *Bulletin de l'Institut Pasteur*, and the *Comptes Rendus de la Société de Biologie* and of the *Académie des Sciences*, as well as the *Proceedings of the Royal Society*, so frequently contain articles on tropical medicine that one almost places them amongst the journals reserved for the special literature of the subject. Sleeping sickness has a journal devoted to it alone, published by the British Sleeping Sickness Bureau. Its functions are to review all of the papers appearing on sleeping sickness and to spread information concerning that disease. One of the best of all of the publications dealing with tropical medicine is, of course, the *Bulletin de la Société de Pathologie Exotique*. Since it has been published, it has taken many of the papers which formerly went to the *Annales de l'Institut Pasteur* and to other French scientific journals. The transactions of the *British Society of Tropical Medicine and Hygiene* always contain extremely valuable papers.

In Great Britain, in the Philippines, in the Congo Free State, in Brazil, and in Portugal, there are institutions, more or less completely, devoted to research in tropical diseases; they periodically publish the results of their work in their own reports. The government and military medical services of, for example, the United States, Great Britain, and India, publish valuable reports; among the best of these are the scientific memoirs of the officers of the medical and sanitary departments of the government of India.

In addition to this huge mass of literature, reports are continually being published from expeditions sent out to study particular points in tropical medicine. Last year no less than

* Paper read before the Johns Hopkins Hospital Medical Society, February 21, 1910.

four important expeditions went to Africa to study sleeping sickness; all of them have issued isolated reports; one of them, in addition, has published a huge volume of 730 pages crammed with interesting information. Laboratories have been established at Khartoum and, more recently, on the West Coast of Africa at Lagos for the study of tropical diseases. The reports of the first named of these laboratories last year filled two large quarto volumes.

During 1909 at least three new text-books on tropical medicine saw the light and new editions of two others appeared. No less than three text-books were published on the pathogenic protozoa, one of them contained 900 pages, and two new handbooks of practical parasitology have been produced.

From this hurried enumeration of the publications dealing with tropical medicine, you will guess that it probably was necessary to winnow a good deal of chaff before it was possible to collect the few grains of corn which I hope to present to you this evening.

A good many papers which are published on subjects connected with tropical medicine are, in truth, chaff of the lightest description. For many years those who, for any reason, found it necessary to write original theses were accustomed to find an easy subject for their papers in the classification and re-classification of the malarial parasites. The work which followed the discovery of "MacCallum's Crow" has brought too much accuracy to our knowledge of malaria. Consequently its parasites are no longer a useful subject for these gentlemen, and many of them have turned their attention, instead, to the newer protozoan parasites. Anyone who tries to look at every paper which appears on, let us say the trypanosomes, the spirochætæ and the piroplasmata, cannot fail to be distressed in realizing how much good time has been wasted, how much good ink has been consumed and how many fair sheets of paper have been spoiled in producing unnecessary re-hashes of well-known facts concerning these parasites.

In 1898 the discovery that malaria is transmitted by the bites of mosquitoes awakened an interest which has resulted in the enormous amount of work on tropical medicine done since then. At first nothing was known of the rôle played by the protozoa, or by other animal parasites, in the production of tropical diseases; and it was most important to ascertain what were the parasites which occurred in tropical climates. Even in our own temperate climate we have come to realize that the diseases of men and of animals have everything in common; in the tropics this statement is truer than it is here. Although a parasite does not often parasitize both men and animals, it frequently happens that one species of a group of parasites is parasitic in man while another species of the same parasite has an animal host. Consequently it has frequently happened that a study of the parasites of lower animals has thrown valuable light upon important points in connection with organisms parasitic in man. For this reason it has been important to ascertain not only what were the parasites of men living in the tropics but it was also necessary to examine animals of all sorts in order to determine what parasites they might contain.

After a few years' work, it became quite apparent that all tropical animals possessed parasites of their own; and it was very evident that, for example, hæmatozoa—which are the most important of the pathogenic animal parasites—were common in almost every species of tropical animal. So soon as this fact was established our needs changed. A catalogue of the parasites infecting tropical animals ceased to be of any great value and the mere publication of the fact that a parasite of a certain appearance had been seen in man or animal was no longer of prime importance. This is especially so since it has become almost certain, from a study of the development of one or two of the pathogenic protozoa, that it is almost impossible to classify a hæmatozoon unless a part, at least, of its life history is known with some accuracy. Again, it has happened that a study of the life cycle of a parasite has led to the devising of measures by which the disease it causes can be successfully combated. For these reasons the greatest need of tropical medicine at the present moment is accurate knowledge concerning the bionomics of the pathogenic protozoa. In spite of this, perhaps because it is much easier, many observers are still spending their energies in mentioning the occurrence of parasites in strange beasts without making any attempt to ascertain how they get there.

I do not intend to speak of any of those tropical diseases which are caused by bacteria, or by food intoxication, as, for example, Malta fever, beri-beri, or pellagra; neither do I intend to mention any of those diseases which are caused by molds or fungi, and nothing will be said of the diseases produced by metazoan parasites. We shall consider only the pathogenic protozoa and our time will be almost altogether occupied by a consideration of the most important of them—the hæmatozoa. We shall, first of all, take a general view of the work done in the whole field of tropical medicine. We shall then consider what advances have been made in the technique employed in the investigation of tropical diseases and, lastly, we shall allude to the advances which have been made in our knowledge of a few particular diseases. I hope that I may be forgiven if I spend most time upon those which seem to me to be most important.

Through the publication of text-books and papers on subjects connected with tropical medicine and through the establishment of schools of tropical medicine, the number of well-trained medical men who practise their profession in the tropics has been greatly increased. One result of this increase has been that the existence of unusual diseases has been recognized in many new localities. For example, during the past year, Malta fever has been reported from the Upper Nile and from Marseilles; relapsing fever has been reported from Colombia, where it is transmitted by the bite of a tick of a different species from that which transmits the same disease in Africa. Relapsing fever has also been reported from Northern Africa. Kala-azar has been shown to exist in Northern Africa, in Italy and possibly also in Greece; while Delhi boil has been seen in several localities in Brazil, in Greece, and in Algiers.

Perhaps the most striking additions made to our knowledge of tropical medicine during 1909 have been (1) the dis-

covery of infantile kala-azar in Northern Africa and the work which has resulted from it; (2) the discovery of a new human trypanosome transmitted by a *Conorhinus* in South America; *and* (3) the knowledge which has made it almost certain that *Trypanosoma gambiense* does undergo a development in the tsetse fly which transmits it. (4) Typhus fever is perhaps not, strictly speaking, a tropical disease, but the fact that it can be transmitted to monkeys by the bites of body lice ought to be mentioned here, as well as the observation that a disease of Southern Austria, which greatly resembles dengue, is transmitted by the bites of a small fly (*Phlebotomus pappataci*).

Although no very extraordinary addition has been made to our knowledge, a great mass of work has been done during the past year on subjects connected with tropical medicine and much has been done to consolidate and coordinate what is known concerning them. Governments seem to have realized more completely than ever that the opening up of the tropics and their colonization by European races is entirely dependent upon the conquest of tropical disease; tropical countries cannot be colonized by Europeans until efficient means have been found of combating the maladies which make warm climates uninhabitable for Europeans. That governments do realize these facts has been shown by the active support which has been given to already existing institutions devoted to tropical research and by the establishment of new ones. For example, the government of Queensland has just established a laboratory for the investigation of the diseases occurring in Northern Australia; another example is the Commission of Entomologists which has just been appointed by the British Colonial Office to study insects which are connected with the transmission or production of diseases of men, animals, and plants in Africa. It is well that governments are alive to the importance of the study of tropical diseases and that new institutions are being maintained in many parts of the tropics for studying them; it is essential for the advance of our knowledge concerning these diseases that this should be the case because many of them are extremely chronic and our knowledge of them has reached a stage where it is almost impossible to advance it without studies lasting over periods of many months or even years. Continued work of this sort can only be undertaken by an institution; the length of time it requires and its tedious nature provide the best excuse for those individual workers who are contented with reporting the existence of a parasite in a host and who make no effort to ascertain something concerning its bionomics.

An enormous number of animals of all sorts have been examined during the past year to ascertain whether they were infected by hæmatozoa; as a result of this work, the presence of these parasites has been described in a great number of animals. One of the most complete pieces of work of the year was done upon a hæmogregarine of the rat by Miller; he described the parasite very carefully and fully worked out the most interesting cycle of development by which it is transmitted from rat to rat by means of the bite of a rat mite. An extraordinary number of trypanosomes have been reported in the blood of fish and other cold-blooded animals, in birds and in mammals. Most of these trypanosomes have occurred in tropical animals, but trypanosomes have been found in the blood of wild rabbits in Scotland and in the blood of wild rabbits and bush rats in Canada. Large trypanosomes, possibly forms of *Trypanosoma theileri*, have been seen in the blood of cattle in Germany, in the United States and in Canada. Some of the amœbæ and flagellate parasites which exist in the alimentary canals of small animals and of insects have received considerable study. New facts concerning an interesting disease of fowls, which is caused by a spirochæta and transmitted by a tick, have been obtained in Brazil, in Roumania, in the Soudan and in Senegal. One form of Leishmania, the parasite causing kala-azar, has been frequently found in African dogs and another parasite of the same species has been seen in African rodents. Some observers have found support for Schaudinn's famous observations on the alternation of generations in the occurrence of a parasite much resembling a trypanosome which has been found within the red blood cells of a South American edentate, and in the fact that one observer has stated that, in fresh preparations, he saw a living trypanosome of the lizard transform itself into a leucocytozoon. Spirochætæ have been described as a cause of a form of human bronchitis in Ceylon; and in Peru small bodies occurring in the red blood cells have been mentioned as a possible cause of the extraordinary "bleeding warts"—the *Verruca peruviana*.

Although the value of much of this work is comparatively slight, it has, nevertheless, helped to extend our knowledge in at least two directions: through it much has been learned concerning the distribution of parasitic disease and our knowledge of the general rules which govern the life activities of the protozoa has been augmented.

No great advance has been made in laboratory technique: the methods by which we have gained the greatest part of our knowledge of the pathogenesis of tropical disease have been very simple. Patience, a pair of dissecting needles, Romanowsky's stain and a good microscope have been, and for that matter still are, the most important part of the equipment of a laboratory devoted to the investigation of the pathogenic protozoa.

The importance of culture methods in the study of the pathogenic protozoa has been vindicated once more by the reproduction of infantile kala-azar in dogs by means of cultures of its causative parasite. The importance of cultural methods has also been shown by the detection and isolation of *Trypanosoma americanum* in the United States in cattle in which the existence of a trypanosome was not suspected. An important change in the ideas governing research work on tropical diseases has been the wide-spread realization of the fact that the methods of preparing parasites for microscopic examination, by which they are permitted to dry, are not good methods; if a delicate parasite be allowed to dry, it is subjected to a physical violence which inevitably alters its appearance. If it be desired to study the finest morphological changes in a protozoan parasite, it is necessary that it should

be prepared for examination by the most careful cytological methods. The material studied must be fresh, it must be well fixed, and it must never be permitted to dry, nor must it be subjected to sudden changes of osmotic tension by being quickly passed through solutions of widely differing density. Consequently "wet methods," by which preparations are not allowed to dry while they are being fixed, stained and mounted, have come to be generally used in the study of the pathogenic protozoa. The spread of the realization of the vital importance of studying living parasites in fresh preparations has constituted another advance in our laboratory methods. The majority of those who study the parasites causing tropical diseases have come to realize that the observation of an actual occurrence in a living parasite is definite and conclusive and that such an observation outweighs any number of observations, apparently negating it, which have been made from fixed material. This fact is probably a partial cause of the present tendency to accept, at least part of, Schaudinn's observations on the alternation of generations in the development of *Hæmoproteus noctuæ* and of *Leucocytozoon ziemanni*.

It will be remembered that in 1903 Schaudinn published a paper in which he described complete life cycles in each of these parasites. The forms of the parasites which had been previously known were both parasites of the red cells of the birds with which he worked; Schaudinn described extracellular, flagellate, forms for both of them; the hæmoproteus became a trypanosome and the leucocytozoon a spirochæta. Schaudinn's work met with a great deal of criticism; many observers did not hesitate to assert that he had been led astray by the existence of other parasites which are frequently present in birds and in the gut of mosquitoes and they believed that he had confused at least two, if not more, parasites in his description of the development of hæmoproteus and of the leucocytozoon. Schaudinn was, of course, a most careful and a most brilliant observer; in his memoir he definitely stated that he had seen certain changes take place in fresh preparations. Everybody knows how difficult it is to prove a negative; and one definite, positive, observation made by Schaudinn will outweigh a great number of negative observations made by less competent observers. This is particularly the case when the question is one concerning the pathogenic protozoa. Because, even under the most favorable circumstances, the most extraordinary patience is often necessary before, even fairly common, developmental forms of a protozoan parasite can be demonstrated.

Much of the work on tropical medicine has been done by medical men who are accustomed to work with bacteria; results are usually obtained much more quickly from work of this sort than from work done on the protozoa; consequently, many of the papers on tropical medicine which report negative results, and some of those which report positive conclusions, are evidently the result of work done with so little patience that one hesitates to accept their findings until they have been substantially confirmed. It is for these reasons that Schaudinn's conclusions have not been totally discredited although an enormous number of papers have been written to assail them.

The bibliography of sleeping sickness which has just been published by the Sleeping Sickness Bureau constitutes one of the most important works done on this disease during 1909; because of it, it is possible to say that our knowledge of sleeping sickness is better marshalled and more easily accessible than is the case with any other disease. Although no vital advance has been made in our knowledge of sleeping sickness, many small observations have been made which, when added to what was already known of the disease, give us a very fair knowledge of human trypanosomiasis and of the way in which it is transmitted. It seems as though there is no weak point by which the disease may be successfully combated as is the case with yellow fever and malaria; it seems to be one of those diseases which must be prevented, not by any one method, but by several. The work which has been done on sleeping sickness during the past year has been in three main directions: (1) the habits of the fly, *Glossina palpalis*, which transmits the disease have been studied in order to ascertain whether it would be possible to prevent the disease by exterminating it. At the same time a good many observers have tried to determine whether the trypanosome undergoes a developmental cycle in the body of the fly; (2) Ehrlich, and his co-workers, have been the foremost among a large number of persons who have made experimental and clinical attempts to treat the disease; (3) those who have been in charge of districts which were threatened by an epidemic of sleeping sickness have been particularly interested in the methods by which the disease might be most certainly and most quickly recognized.

Glossina palpalis is the most usual agent by which the disease is transmitted; a good deal has been learned about its habits. It was already known that it only lived near water and in localities where there was thick brush. The reason for this has been found in the fact that the singly deposited pupæ of the fly will not develop unless they are kept in a humid atmosphere and unless they are protected from the sun. These facts make it evident that all persons living in an infected country should avoid the neighborhood of water as much as possible and that watering-places and ferries, to which people must come, should be kept free from underbrush in order that there may be no shelter for the flies in their vicinity.

A good deal of work, which has resulted in no definite conclusion, has been done to ascertain whether *Trypanosoma gambiense* can be transmitted from man to man by other means than by the bite of *Glossina palpalis*. At the commencement of last year, most persons believed unquestioningly that the fly could only transmit the trypanosome if it had bitten an infected person not more than 48 hours previously. But when one considered the small quantity of blood ingested by each fly and the scantiness of trypanosomes in the blood of persons suffering from sleeping sickness, it became quite evident that the rapid spread of the disease in areas where it was epidemic could not be accounted for if

Glossina palpalis only transmitted the disease mechanically; that is if its proboscis merely acted as a hollow needle and if there were no development of the trypanosome within the fly. On entirely insufficient grounds Koch suggested that this discrepancy between the rapid spread of the disease and the inefficiency of the mechanical means of transmission might be accounted for through a transmission of the trypanosome by coitus. It has been shown since, that *Trypanosoma gambiense* may be mechanically transmitted by the bites of mosquitoes and it does not seem to be at all impossible that something of the rapid spread of the disease may be accounted for in this way; this explanation is scarcely needed now since it is very probable that a development of the trypanosome does occur within the fly because both the German and British expeditions have shown that *Trypanosoma gambiense* can be transmitted by *Glossina palpalis* up to a period of 75 days after the fly has fed upon an infected animal.

Although many observers have described appearances in preparations made from the gut of infected flies, which might be developmental forms, nothing definite can be said concerning them at the present time because of the frequency with which tsetse flies are infected with other flagellate parasites. Although flagellate parasites of the same sort frequently occur in the gut of the rat louse, it is practically certain that the ordinary trypanosome of the rat—*Trypanosoma lewisi*—does undergo a definite development in the body of the louse, by which it is transmitted. Some of the forms which have been described in the proboscis and in the alimentary canal of tsetse flies infected by *Trypanosoma gambiense* greatly resemble those which occur in the development of *Trypanosoma lewisi* in the rat louse. For this reason, and because of the length of time that the fly is infected after it has bitten an infected animal, it seems almost certain that *Trypanosoma gambiense* must undergo a development within the body of its invertebrate host. It is useless to speculate at present upon the nature of this development or to hazard a guess as to whether it is sexual or a-sexual.

A point well worth noting here is that not every fly which has bitten an infected person is capable of transmitting the infection after the lapse of 48 hours. A similar observation has been made in connection with the transmission of *Trypanosoma lewisi*. The development of the trypanosome does not occur in the body of every louse which has fed upon an animal infected with *Trypanosoma lewisi*. It is only when the trypanosomes are at a particular stage when they are ingested that the development occurs and it does not seem at all impossible that something of the same sort may occur in the transmission of *Trypanosoma gambiense* by *Glossina palpalis*. It may be that the development of the trypanosome does not occur in the fly unless the trypanosomes are ingested at a particular stage of their development. An analogy drawn from the well-known fact that only the adult male and female forms of the malarial parasite will develop within the body of an appropriate Anopheles suggests itself; and one asks whether it may not be that it is only in old-standing infections that *Trypanosoma gambiense* exists in man in a form suitable for undergoing a development within *Glossina palpalis*. The developmental change which the mammalian trypanosomes undergo, most frequently, in the circulation of their vertebrate host is a multiplication by binary division; but, it has long been known that these trypanosomes sometimes undergo a change in which the whole of the locomotary apparatus is lost. The analogy of a developmental cycle of the frog trypanosome suggests that this stage may be the first step in a process of multiplication of a different sort. In the frog trypanosome the flagellum, the undulating membrane and the blepharoblast are cast off. The organism becomes rounded and rapidly subdivides, dichotomously, until sixty or more small spheres result. Each of these divisions produces an undulating membrane and a flagellum, and passes through a herpetomomas-like stage to become a trypanosome. An observation made upon *Trypanosoma cruzi*, the new South American trypanosome, suggests that the supposition may be correct and that such a cycle of multiplication does exist in mammalian trypanosomes; it has been shown that *Trypanosoma cruzi* casts off its locomotary apparatus, becomes spherical and then divides so as to produce several new trypanosomes.

Through his work on the treatment of experimental trypanosomiasis, Ehrlich has arrived at far reaching conclusions in his study of "Chemical Constitution and Therapeutic Reaction." As he says himself, he hopes to see a day come when medical men will be in a position to "aim chemically" with the drugs which they administer in the treatment of disease. Ehrlich believes that the trypanocidal compounds of arsenic, which he has produced, owe their property of destroying trypanosomes to the fact that reduction has reached an extreme point in them. This view has not the complete support of those who believe that the trypanocidal effect is due to the formation of a body, called trypan-atoxyl, by a combination between the drug administered and some albuminous substance existing in the body of the host. Again, Ehrlich's view is directly combated by others who believe that atoxyl, for example, is oxidized in the bodies of animals treated by it. The practical result of the year's work on the treatment of human trypanosomiasis is that several, highly trypanocidal, compounds of arsenic have been produced and that preparations of antimony—particularly para-amido-phenyl-stibnic acid and tartar emetic—have been shown to be highly trypanocidal. At the present moment, the position in the treatment of human trypanosomiasis is this: the treatment is a dangerous one because the large doses of atoxyl necessary not infrequently cause neuritis, particularly optic neuritis and consequent blindness, but the treatment should nevertheless always be tried because it does offer a good chance for the recovery of early and thoroughly treated cases. Atoxyl and its derivatives are the most important of the trypanocidal agents. They are to be given in as large doses as possible and as early in the infection as possible. They should not be given in small doses or during a considerable period of time lest the trypanosomes become resistant to them. After a severe course of atoxyl has been given, the drug should be stopped and some

other trypanocidal drug should be given in order that the treatment may be a combined one; it has been definitely proved by experiments on animals that treatment by two trypanocidal drugs offers a greater chance of success than does treatment by a single one.

Long before Europeans commenced to study sleeping sickness, the natives of the West Coast of Africa realized that persons who had much enlarged neck glands very often died from sleeping sickness. From an investigation of the incidence of definitely enlarged glands among natives in the Congo Free State, it was concluded that every negro, suffering from enlarged glands, in an area where human trypanosomiasis existed, should be suspected of being infected with *Trypanosoma gambiense* until the contrary could be proved. This assertion at first met with a good deal of opposition but its accuracy has been confirmed by the results of the observations of the French Sleeping Sickness Commission and by the work done by an expedition sent out by the Liverpool School of Tropical Medicine to study that disease in British Central Africa. Now it is generally recognized that every native should be most carefully examined for trypanosomiasis if he be the subject of a glandular enlargement. This observation is exceedingly important because the history of the extension of sleeping sickness shows that it has been spread through Africa by the introduction of cases of the disease into formerly uninfected areas. By the establishment of modified quarantines in which cases of the disease will be isolated and treated, it is hoped that it will be possible, if not to prevent the existence of the disease, at least to delay its spread until more efficient means of combating it have been devised.

Leishman has confirmed the cycle of development of *Spirochæta duttoni* which the Liverpool observers described in the body of the tick, *Ornithodoros moubata*. It will be remembered that this spirochæta was observed to undergo approximately the same development in the bodies of its vertebrate and invertebrate hosts. It becomes coiled into a tight skein, its chromatic core fragments and new spirochætæ probably arise from the encysted chromatic masses which are thus produced. Leishman, in addition to confirming this development, has shown that the granules thus produced are infective when inoculated into experimental animals.

Additional support for this life cycle has been found in the study of *Spirochæta gallinarum*, which is transmitted from fowl to fowl by the bites of the tick *Argas persicus*. This spirochæta, like the *Spirochæta duttoni*, may enter the red cells of its vertebrate host; and, in the tick, it produces granules similar to those formed by *Spirochæta duttoni* in the human tick.

Relapsing fever is rather a dangerous disease to work with because of the numerous cases of laboratory infection which occur. A possible explanation of these cases, which formerly could not be accounted for, lies in the fact that *Spirochæta obermeiri* may be transmitted by rat lice.

Most of the publications which have appeared on malaria during the past year have dealt with the prevention of the disease. The methods by which malaria may be prevented, through the extermination of mosquitoes and through the destruction of the parasites in the human hosts by the public distribution of quinine, are familiar to everyone. The most efficient methods by which the principles of malaria prevention may be applied in communities of various types are rapidly becoming systematized. An excellent example of the complete success which follows an intelligent and thorough enforcement of anti-malarial measures is afforded by the health of the laborers employed upon the Panama Canal; the incidence of disease amongst those living in the Canal Zone is actually less than it is amongst the population of New York. Campaigns for the prevention of malaria have been carried on with almost equal success in other parts of the world; for example, mosquitoes have been practically exterminated at Port Said. It is interesting to note, in passing, that dengue fever has disappeared from Port Said with the mosquitoes; it was, of course, known that dengue fever could be transmitted by a Culicine mosquito. The French have realized that the success of their colonies in Northern Africa depends completely upon the prevention of malaria in them; and, consequently, the government has taken active measures against that disease. The extermination of mosquitoes is an important part of their propaganda but, as in Italy, those in charge of the campaign seem to lay especial weight upon the importance of cinchonizing the population through the distribution of quinine; a good deal has been written in Italy concerning the preparation of quinine which is best for public distribution. Because it has almost no taste and because it is easily absorbed, the tannate of quinine, prepared in chocolate tablets, seems to be the best form of the drug for this purpose.

Several important papers have appeared on blackwater fever. None of them have reached an absolute determination of the cause of blackwater fever, although a concensus of their opinions certainly supports the usual theory that blackwater is in some way the expression of an intoxication produced by chronic malaria. Consequently, if malarial parasites are present in the blood of the patient, quinine must be given; but, since quinine may sometimes precipitate a hæmoglobinuria, the drug must be given in small doses (2 grains); these doses are to be repeated, if necessary, at frequent intervals.

With the exception of the discovery of the infantile form of kala-azar, no particularly important addition has been made to our knowledge of that disease or of the parasite, *Leishmania*, to which it is due. The developmental stages of *Leishmania* formed in cultures by the parasite of kala-azar and by the nearly related parasite of oriental boil have been seen by several observers. No certain light has been thrown upon the possible relationship of these two diseases; it is interesting to note, however, that forms almost identical with *Leishmania donovani*, the parasite of kala-azar, have been found in the circulating blood of a patient suffering from an oriental boil, in which typical forms of *Leishmania furunculosa*, the parasite of oriental boil, had been demonstrated. The methods by which these diseases are transmitted have not been as-

certained although it has been suggested, not without grounds, that bed bugs—or perhaps a *Conorhinus*—might be the transmitters. Attempts at the treatment of kala-azar have been made and in some instances patients have undoubtedly improved under the administration of atoxyl; it is too early yet to say whether it is probable that this improvement may be a permanent one.

Very little has been added to out knowledge of yellow fever. Thomas succeeded in producing a distinct reaction, accompanied by fever and other symptoms, in chimpanzees and in guinea-pigs which were bitten by infected mosquitoes. Thomas believes that the illness produced by the bites of mosquitoes in these cases was yellow fever, and consequently, that it has been proved that the lower animals may suffer from that disease. If his conclusion proves to be correct, the observation is an important one.

A great deal has been written about the dysenteries, particularly about amœbic dysentery, and about the parasites which cause them; we shall say nothing of the bacillary dysenteries. An interesting observation is that there are apparently healthy "amœba carriers" just as there are apparently healthy typhoid carriers. An interesting treatment of chronic dysentery has been advocated by those who suggest that an appendicostomy should be done and that the opening should be utilized in applying frequent, copious douches to the whole course of the great bowel. The pathogenic properties of *Balantidium coli* have been once more proved by the observance of a severe dysentery produced by this parasite in monkeys; while *Lamblia intestinalis* has again been described as a probable cause of Cochin China diarrhœa.

Although it has so far been without practical result, one of the most interesting features of the year's work, in as much as it shows the probable trend of much of the future work on the pathogenic protozoa, has been the enormous number of papers which have appeared on subjects connected with the immunity which may be acquired against protozoan parasites. The position of our knowledge is, approximately, this: that an immunity—if not a "sterilizing immunity" at least a tolerance—may be acquired by many mammalian hosts to the presence of protozoan parasites. For example, those who have lived for many years in malarious districts may have the parasites of malaria in their bodies without suffering any apparent ill effects; just in the same way, some wild animals, and even cattle and, possibly, men, may live for many years with pathogenic trypanosomes circulating in their blood; while both in America and in the Tropics cattle infected with piroplasmata live healthily for years. In all of these diseases the "resistance" of the host, from some undefined cause, may be suddenly lowered. Then the host seems to be no longer able to resist; the parasite multiplies and produces an acute attack of the disease with which it is associated. The question which is to be solved is, what is the mechanism by which these hosts are able to keep the parasites infecting them in check for so long? The papers which have appeared so far have barely touched the fringe of the question and have made no attempt to reply to it. When it is answered, it is probable that it will bring us some indication of the direction which work must follow which has for it object the devising of means of preventing protozoa-caused diseases through the production of active or passive immunity in the hosts.

ANAPHYLAXIS AND ITS RELATION TO CLINICAL MEDICINE.*

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It was with much pleasure that I accepted the invitation of your secretary, Dr. Moss, to speak to the Medical Society of the Johns Hopkins Hospital upon the subject of anaphylaxis. In addition to appreciating the honor of the invitation of your secretary I was especially pleased to come, in view of the fact that the first paper that was presented in America upon the subject of anaphylaxis was one by Dr. Rosenau and myself, before the Association of Pathologists and Bacteriologists in this city in the spring of 1906.

The Johns Hopkins Medical School bears a peculiar relation to the subject of anaphylaxis in that Prof. von Pirquet, now professor of pediatrics at Johns Hopkins University, was the first to call attention to the manifestations of anaphylaxis in the human being. His work gave us our first understanding of the unpleasant serum reactions, and to him we owe a new disease—the serum disease.

In most of my work upon anaphylaxis up to this time I have been associated with Dr. Rosenau, and my remarks will be based largely upon this joint work.

The earliest experimental work upon the subject was that by Richet, working with actinia poison in dogs. Richet coined the word "anaphylaxis" from two Greek words ἀνά against, and φύλαξ guard, or φύλαξις protection. He considered the condition an opposite one to that of prophylaxis; but we now know that the phenomenon, instead of being a disadvantage, is probably an important step in the protection of the organism against a certain large class of infections.

The condition of anaphylaxis may be transmitted from the mother or may be acquired, and it may be brought about by the introduction of any strange proteid into the body. A well known clinical instance of anaphylaxis is that induced in an individual by a second vaccination. In the reaction to a primary vaccination the incubation period is about four days, *i. e.*, in about four days the local symptoms at the point of

* Read before the Johns Hopkins Hospital Medical Society, March 7, 1910.

vaccination appear or become distinctive and there is a more or less constitutional disturbance. In a secondary vaccination, or a vaccination following a successful vaccination after some months, the period of incubation is much shortened and the clinical reaction very much lessened. In other words, the power to react has been so changed that, instead of an incubation period of four days, we have an incubation period of 24 or 36 hours. This acquired power of immediate response is an evidence that protective bodies have been formed within the organism; but there is no absolute immunity in this class of infections though, on account of the power of immediate reaction, the individual is protected.

Other well known clinical instances of anaphylaxis are the tuberculin and mallein reactions in tuberculosis and glanders. Neither of these bacterial products is harmful in moderate amounts to a healthy individual, but a person suffering from tuberculosis or glanders will respond to a very small amount of tuberculin or mallein respectively.

It has been known since the seventeenth century that the whole blood of certain animals is poisonous when transfused or injected into man. Many workers have found that the blood serum of an animal of one species is frequently poisonous when injected into an animal of another species, but that the serum of the horse and the donkey to a large extent lacks such poisonous properties. Large amounts of horse serum may be injected into man, the rabbit, the guinea-pig and other animals without causing very unpleasant results except possibly a slight reaction at the site of inoculation. In a certain proportion of cases, however, the injection of horse serum into man is followed by the syndrome described and named by von Pirquet as the "serum disease." In a very small percentage of cases the injection of horse serum into man has been followed by sudden death.

Horse serum, when injected into guinea-pigs, is a comparatively bland and innocuous substance, but these animals may be rendered so sensitive that a second injection of horse serum may produce death, or at least very severe symptoms.

If a guinea-pig be given 0.001 cc. horse serum and 14 days later a second injection of a larger amount the result is almost invariably fatal. The same will be true if the animal at the two injections be given some other protein such as eggwhite or milk, or some vegetable protein such as edestin or excelsin.

The first injection of the foreign protein has so changed the mechanism of the animal's organism as to render it very susceptible to the second injection. A certain time must elapse between the first and the second injection in order that this hypersusceptibility may be manifested. This time varies from 5 to 12 days and is in close accord with the period of incubation of the "serum disease" which von Pirquet places at 8 to 13 days.

As the first experimental work with anaphylaxis was done with horse serum it was thought that diphtheria antitoxin had some part in this toxic action of the serum; but as it was soon found that the phenomenon could be induced by any protein, such as those which have just been named, it was seen that diphtheria antitoxin had absolutely no part in the production of the phenomenon.

The toxic action following the injection of the serum is due to a protein in the horse serum and is entirely independent of the antitoxic properties of the serum. It would be exceedingly unfortunate if the studies upon anaphylaxis should in any way prevent the usage of diphtheria antitoxin, or any other therapeutic serum, when it is indicated.

Most of the studies upon anaphylaxis have been done upon guinea-pigs, using horse serum as the foreign protein. And in discussing the subject I shall speak of horse serum, using it, however, in the sense of a protein.

The symptoms produced by the injection of horse serum into a susceptible guinea-pig are exceedingly characteristic. They are apparently the same, whether the animal be given the injection subcutaneously, intravenously, intraperitoneally or into the brain, with, however, the difference that when given into the brain or into the circulation the symptoms appear very much more quickly and frequently with explosive violence, in some instances the animal dying within three minutes after the injection. Within 5 or 10 minutes when the injection is given intraperitoneally the guinea-pig becomes restless and agitated; it runs about the cage, and sometimes utters sounds of distress; then there appear manifestations of peripheral irritation and respiratory embarrassment as shown by scratching at the mouth, coughing, sneezing, rapid and irregular respiration. An exceedingly characteristic feature of the respiratory involvement is that at intervals the animal makes an unusually deep inspiratory effort with the diaphragm, resulting in a marked sinking at the lower end of the sternum. The stage of excitement is soon followed by one of paresis, or in some cases complete paralysis. The animal is unable to stand and if it attempts to do so it falls upon its side. Spasms or general convulsions may now appear.

Guinea-pigs in a condition of complete paralysis may fully recover, but within a short time convulsions usually begin and are almost invariably a forerunner of a fatal termination. Occasionally in guinea-pigs not very susceptible the onset of the symptoms following an intraperitoneal injection may be delayed 30 or 40 minutes, but in only a few instances have I noted the onset of symptoms delayed as long as one hour.

The chain of symptoms is exceedingly characteristic, but they do not always follow the same order. Death usually occurs following an intraperitoneal injection within 30 minutes. There appears to be no lowering of the animal's temperature during or following the appearance of the symptoms. There is a marked fall in the blood pressure, which goes hand in hand with the respiratory embarrassment. The blood during this stage is very dark in color and there is a tendency to delayed clotting. If, when the respiratory embarrassment is marked, the animal be given artificial respiration there is almost immediately a rise in the blood pressure.

After complete cessation of respiration the heart continues to beat for a long time. In some instances I have noted the heart to beat as long as 30 minutes after complete stoppage of respiration.

Death is apparently due to asphyxia and, as suggested by Auer and Lewis,[1] is probably a result of a tetanic contraction of the muscles of the bronchiolæ and alveolar ducts, thereby preventing the free ventilation of the alveolæ.

The hemorrhages which have been described by some as characteristic lesions in death from anaphylaxis are probably due, not to a rupture of the capillaries, but to an oozing following the very great lowering in blood pressure and are not characteristic of death from anaphylaxis alone.

At least a certain time must elapse between the first and the second injections of the protein before the anaphylaxis is manifest. This time or period of incubation is from 7 to 12 days, which is about the same as for the serum disease in man and is very similar to the period of incubation of a number of the infectious diseases.

I have noticed suggestive symptoms in guinea-pigs when the second injection is given after an interval of four days and have found the animal sensitive after an interval of over three years. The optimum period or interval, however, for the development of anaphylaxis is after three weeks.

If the guinea-pig be given an injection of a foreign protein and then a second injection at any time during the period of incubation no ill results will follow; in other words, there has not been time for the body to become sensitive to the second injection. But if the second injection be given after the 12th day the animal is then found to be acutely sensitive to the second injection, and the result is usually fatal.

There appears to be no difference whether the animal be given the sensitizing injection subcutaneously, intraperitoneally, into the brain or into the circulation, or whether the intoxicating dose be given through the same or through different channels.

In the first paper by Rosenau and myself[2] we suggested that the portion of the protein which sensitizes the guinea-pig is the same as that which later poisons it, and up to the present no work has appeared to cause me to alter this opinion.

Wells[3] has brought forward experimental data to show that the two are at least in the same protein molecule or are two separate portions of the same molecule. Some workers have claimed that as heat and other agents had a different effect upon the sensitizing and toxic principles in horse serum the two principles were different; but it has been shown[4] that, while the toxic and sensitizing action of serum is gradually modified by heat when the serum is in a liquid condition, these principles are practically unaffected when the serum is first dried, then heated, redissolved and used either for sensitization or intoxication.

It would seem that these workers have fallen into the error of drawing conclusions as to the different effect of various agents upon the sensitizing and poisoning properties of proteins by overlooking the fact that, while it requires a very minute amount of the protein to sensitize, it requires considerably larger amounts to intoxicate the guinea-pig; and if a portion of the anaphylactic-producing properties of the protein is destroyed by some means there might be enough left to sensitize an animal in certain amounts but not enough to intoxicate except in amounts very much larger than those commonly used.

The effect of heat in modifying or destroying the anaphylactic properties of proteins depends upon its effect, as suggested by Wells[5] and later proved by Anderson and Rosenau,[6] in rendering the proteins insoluble rather than by the production of chemical changes in the proteins. For example, if the horse serum be heated in the liquid state, its sensitizing and intoxicating properties are gradually lessened by heating from 60° C. until at 100° C. they are practically destroyed. But if the serum, and the same is true of a protein such as eggwhite, be thoroughly dried, it may then be heated to temperatures as high as 170° C. for 10 minutes or 130° C. for two hours without affecting to any appreciable extent its anaphylactic properties when redissolved in salt solution and injected into a guinea-pig.

Neither sensitizing nor toxic principles in proteins are affected by various substances such as calcium chloride, sodium nitrate, magnesium sulphate, ammonium sulphate, formaldehyde, pancreatin, rennin, invertin, emulsin, malt, etc., nor by freezing, filtering through porcelain, precipitation and dialysis, or exposure to the X-rays.

Lewis and Auer[7] reported that atropine appeared to have a favorable influence upon the outcome of anphylaxis when given a short time previous to the intoxicating injection. With Dr. W. H. Schultz, of the Hygienic Laboratory, I have been able to confirm to a certain extent these observations; but apparently the amount of atropine needed for guinea-pigs is so large that it does not seem to promise much for its practical use in man when used in individuals known or suspected of having an idiosyncracy for horse serum, but further work with the substance may alter this view.

We[8] have found that, working with very sensitive guinea-pigs, it was possible to save with atropin sulphate about 28 per cent, with injections of chloral hydrate plus urethane and adrenalin 41 per cent, by administering pure oxygen 43 per

[1] Auer, J., and Lewis, Paul A.: Acute anaphylactic death in guinea-pigs; a preliminary note. J. Am. M. Ass., 1909, Vol. LIII, p. 458.

[2] Rosenau, M. J., and Anderson, John F.: A study of the cause of sudden death following the injection of horse serum. Hygienic Laboratory Bulletin, No. 29.

[3] Wells, H. Gideon: Studies on the chemistry of anaphylaxis, I. J. Infec. Dis., 1908, Vol. V, p. 449.

[4] Anderson, John F., and Rosenau, M. J.: Further studies upon the phenomenon of anaphylaxis. J. Med. Research, 1909, Vol. XXI, pp. 1-19.

[5] Wells, H. Gideon: Studies on the chemistry of anaphylaxis, I. J. Infec. Dis., 1908, Vol. V, p. 449.

[6] Anderson, John F., and Rosenau, M. J.: Further studies upon the phenomenon of anaphylaxis. J. Med. Research, 1909, Vol. XXI, pp. 1-19.

[7] Lewis, Paul A., and Auer, John: Acute anaphylactic death in guinea-pigs; its cause and possible prevention. A preliminary note. J. Am. M. Ass., 1909, Vol. LIII, p. 458.

[8] Anderson, John F., and Schultz, W. H.: The cause of serum anaphylactic shock and some methods of alleviating it. Proc. Soc. Exper. Biol. & Med., 1910, Vol. VII, pp. 32-36.

cent, and by administering pure oxygen along with chloral hydrate and adrenalin even 66 per cent. Almost invariably life was prolonged, the pigs eventually dying from low blood pressure and not from acute asphyxia.

It requires only a very small amount of horse serum to sensitize a guinea-pig. Amounts as small as 1/1,000,000 cc. will do this, or 1/20,000,000 part of purified eggwhite, while 1/100 cc. of horse serum intravenously or 5/1000 mg. of purified eggwhite are fatal to a sensitive animal.

Besredka [9] has reported that anaphylaxis may be prevented by ether or alcohol narcosis.

Banzhaff and Famulener [10] have also reported that the administration of large doses of chloral hydrate to guinea-pigs prevents death from anaphylaxis in a large proportion of cases.

These procedures have always appealed to me as being theoretically very advantageous, as they might act in one or two ways; either by a blunting of the respiratory center so that it would not respond to the extreme shock of the substances formed by the union of the intoxicating dose and the previously formed antibody, whatever it may be, resulting from the first injection of the serum, or by relaxing the muscular fibers of the bronchioles thus admitting a free exchange of oxygen. But later experiments have shown that these reported results are not borne out by other workers, for the fatal outcome of anaphylaxis is not prevented by ether or alcohol narcosis or by the administration of large doses of chloral hydrate, urethane, or other similar preparations.

From the beginning of my work upon anaphylaxis I was interested in the specificity of the reaction and had often in my mind the possibility of the utilization of this specificity in medico-legal work and also as an aid in the diagnosis of certain diseases by the passive production of anaphylaxis.

For proteins of a very different nature the anaphylactic reaction is absolutely specific, but for proteins more or less closely related, such as that in the serum of a horse and the serum of a dog, the reaction is only quantitatively specific. That is, the animals may respond to an injection of the heterologous serum, but the reaction is never as marked as when the homologous protein is given at the second injection. But there is the possibility that if the passive method be used this reaction, even with related proteins, may be found to be strictly specific.

A very interesting fact in connection with the specificity of the reaction is that guinea-pigs may be sensitized with three proteins at the same time. That is, they may be given a mixture of eggwhite, horse serum and milk at the same time, and then tested for their susceptibility to each one of these substances and found to react after the usual incubation period to a second injection of each substance at intervals of about two hours. In other words, the animal differentiates the anaphylactic-producing substances in a separate and distinct manner and is found to be susceptible to a second injection of each one of the three substances in the same way that an animal is susceptible to three separate infectious diseases.

Gay and Southard [11] discovered that there is a substance in the blood of sensitive guinea-pigs that may be transferred to a normal guinea-pig and render it susceptible to a subsequent injection of the protein 15 days later.

Otto [12] later showed that this passive sensitization was apparent within 24 hours.

Gay and Southard gave the name "anaphylactin" to their principle and considered it a portion or "rest" of horse serum. In this they are probably correct, but the passive sensitizing substance shown by Otto to be present within 24 hours is very probably an antibody. On account of its power of producing a changed reaction and the necessity for a name I should like to propose the name *allergin* for this passive sensitizing principle which is manifest within 24 hours, in contradistinction to the anaphylactin only manifested within 15 days.

It has been found that *allergin* does not appear in the blood of sensitized guinea-pigs until the 9th or 10th day, *i. e.*, just about the expiration of the period of incubation. It is found not only in the blood of sensitive guinea-pigs, but in the blood of guinea-pigs that have received a number of injections of serum sufficient to render them either immune or extremely refractory to a single large injection.

From this it would appear that there can be produced a cellular immunity to anaphylaxis, while the sensitizing substance (*allergin*) is present in the flowing blood, the organism as a whole or its susceptible cells being protected by a neutralizing antibody.

When guinea-pigs are sensitized with three proteins at the same time, three separate *allergins* may be demonstrated.

Many workers have studied the question as to the presence of an antibody in the blood serum of sensitive guinea-pigs, but without having satisfactorily demonstrated its presence.

One of the most interesting facts brought out in our studies upon anaphylaxis and which, in my mind, has been much neglected in later work upon the problem, has been the sensitization of guinea-pigs by feeding them for several days on the foreign protein. Guinea-pigs may readily be sensitized by feeding them a protein for several days; when tested for their susceptibility after 14 days by an injection of the protein they are found to be sensitive.

Wells [13] has found that the specificity is lost when certain proteins are fed to men, their urine collected and used to sensitize guinea-pigs. He found that when alimentary albuminuria is produced in man by feeding raw eggs and the urine of the individual used to sensitize guinea-pigs, the latter animal will not respond to a second injection of eggwhite, but develops anaphylaxis when given an injection of human ascitic fluid. This has an important relation to the sensitization of

[9] Besredka, A.: Comment peut-on combattre l'anaphylaxie? Ann. de l'Inst. Pasteur, 1907, Vol. XXI, p. 950.

[10] Banzhaff, E. J., and Famulener, L. W.: A note on anaphylaxis. Proc. Soc. Exper. Biol. & Med., 1908, Vol. LXII.

[11] Gay, Frederick P., and Southard, E. E.: Serum anaphylaxis in the guinea-pig. J. Med. Research, 1907, Vol. XVI, p. 143.

[12] Otto, R.: Zur Frage Serum-Ueberempfindlichkeit. Münch. med. Wchnschr., 1907, Vol. LIV, p. 1665.

[13] Wells, H. G.: Alimentary albuminuria by means of the anaphylaxis reaction. J. Am. M. Ass., 1909, Vol. LIII, p. 863.

animals by feeding them with the foreign protein, and may give us some insight as to why certain individuals have a peculiar idiosyncracy for certain articles of diet; also, why certain individuals who have never previously received an injection of foreign protein should be so acutely sensitive to a first injection of horse serum.

Another exceedingly interesting point brought out in the early work was as to the maternal transmission of anaphylaxis. It was found that the young of a female guinea-pig which had received an injection of horse serum, either before or after conception, were acutely sensitive to an injection of the same protein. This transmitted sensitiveness is solely maternal; the male takes no part in it.

The milk has been excluded as a factor in this transmitted susceptibility by a number of exchange experiments, which consisted in placing the young guinea-pigs born of a susceptible mother to nurse with an untreated female and, in exchange, the young of the untreated female to nurse with a susceptible female. From these experiments it was learned that the hypersensitiveness is not transmitted in the milk.

These experiments upon the transmission of anaphylaxis by the female to her young are of very great interest in relation to the question of an inherited tendency to tuberculosis in children born of a tuberculous mother. It is generally accepted, I believe, that the children of a tuberculous mother, instead of having an immunity to tuberculosis, on the other hand are more susceptible. I think it can be stated positively that only very rarely is the child born with the seeds of the disease in its system, but that there is transmitted from the mother to her offspring a tendency to the disease.

There appears to be a very close analogy between the tuberculin anaphylaxis and the anaphylaxis produced by the injection of proteins. The one is an anaphylaxis produced by the products of bacteria growing in the animal body, and which may be manifested by an injection of the products of the same bacteria growing outside the body; the other is an anaphylactic condition produced by the injection of a protein, and may be shown after a certain interval by a second injection of the same protein.

In the case of protein anaphylaxis this hypersusceptibility is transmitted by the mother to her young. In the case of tuberculosis the disease itself is not transmitted by the mother to her offspring, but the tendency to the disease is. I think here is a very promising field for work.

In certain cases in which the mother has received an injection of serum before the birth of the child a hypersensitiveness may be transmitted to her offspring, and this may explain some of the severe primary reactions in children.

There can be hardly any question but that man may be sensitized in the same way as has been shown to be the case with guinea-pigs. Repeated injections of horse serum into man at intervals of days, months or even years are not infrequent. Persons exposed to or suffering with repeated attacks of diphtheria are given injections of antitoxic serum at short or frequent intervals. It is not unusual for persons to have several attacks of diphtheria at longer or shorter intervals or to be exposed to diphtheria, and to be treated each time with diphtheria antitoxin.

The method of use of certain sera, as for example the antitubercule serum of Maragliano, require their administration at intervals of days or weeks continued over a long period of time. In all these cases of repeated injections the amount which has been injected, the interval between the injections and the number of injections must be taken into consideration. von Pirquet and Schick,[14] in their work upon the serum disease, found that when the second injection was given after an interval of 14 days to four months they obtained what they termed their "immediate" reaction, in which the symptoms of the serum disease appeared at once or within 24 hours; but that when the interval was more than four months, they obtained little or no immediate reaction but what they termed the "accelerated" reaction, in which the symptoms of the serum disease appeared on the 5th, 6th, 7th, or 8th days. It will be remembered that the usual period of incubation is from 8 to 13 days.

Guinea-pigs show practically no reaction following a single injection of serum, while in man the symptoms of the serum disease may appear after an incubation period of 8 to 13 days. Both man and the guinea-pig react to a second injection; the reactions in man and the guinea-pig, however, differ to some extent both in severity and in kind. The reaction following a second injection into the guinea-pig is, to a large extent, borne by the respiratory system, whereas in man the reaction is shown locally at the point of inoculation, by fever, by joint pains, swelling of the lymph nodes, and albuminuria. In a few cases in man, however, the reaction is very similar to that in the guinea-pig and these cases are the alarming ones.

In rabbits the reaction is rarely manifested after a second injection, but may be brought out by repeated injections at intervals of days. Some of the fatal cases in man, other than those following the first injection, have been in persons who have received repeated injections at intervals of days over a period of some time, thus being somewhat similar to the reaction in the case of the rabbit.

It was suggested by Besredka[15] that there might be a relation between the toxicity of serum, as tested upon guinea-pigs, and its power to produce the serum disease in man. But work by others has shown that the symptoms of the disease depend largely upon the amount of serum used and the interval between the injections. The unfortunate accidents, such as collapse and sudden death, depend to my mind more upon individual sensitization than upon the so-called toxicity of the serum used. It has been found that serum which has not produced untoward symptoms when injected into man is fully as toxic for sensitive guinea-pigs as serum, the use of which has been followed by serious symptoms or even sudden death when injected into man. As before stated, I believe it de-

[14] von Pirquet, C., and Schick, B.; Die Serumkrankheit. Leipzig, Franz Deuticke, 1905, 144 p.

[15] Besredka, A.: Toxicité des sérums thérapeutiques, sa variabilité et son dosage. Ann. de l'Inst. Pasteur, 1907, Vol. XXI, p. 777.

pends upon the susceptibility of the individual and not on the toxicity of the serum.

It has been a most interesting fact, in this connection, that many of the cases of sudden death following the first injection of serum in man have been in asthmatics or in persons who have an idiosyncracy to horses. That is, there are certain individuals who show peculiar symptoms, sometimes resembling hay fever or asthma, when in the vicinity of horses or horse stables; and these individuals are the ones who are so extremely susceptible to a first injection of serum. The knowledge of the fact that the injection of horse serum into such persons is a danger must certainly be taken into consideration in the use of antitoxin.

Anaphylaxis having been produced by various proteins, and the similarity of the tuberculin and the mallein reactions to protein anaphylaxis, early suggested the possibility of the production of anaphylaxis by bacterial extracts. It was thought that perhaps following anaphylaxis produced by bacterial extracts, there might be an immunity to the corresponding bacteria. In certain instances this has been found to be true.

I am of the firm opinion that the phenomenon of anaphylaxis has an important relation to the prevention and cure of certain specific processes and that resistance to certain diseases is largely gained through the processes of hypersusceptibility, and this opinion is certainly strengthened by the immunity which follows a hypersusceptibility developed by bacterial extracts. It is not more than a coincidence that the time required for the development of anaphylaxis corresponds very closely with the period of incubation of a number of infectious diseases and with the period of incubation of the serum disease.

In certain diseases with short periods of incubation, such as pneumonia, the crisis which commonly appears about the 8th to the 10th day may find a somewhat similar explanation.

It is also equally evident that those diseases produced by soluble toxins, such as diphtheria and tetanus, do not belong to this class.

It is very evident from the above rather incomplete review of the subject of anaphylaxis that studies upon this phenomenon are of more than theoretical interest and value, and that a satisfactory explanation of the mechanism of anaphylaxis will give us a clearer insight into the cause of recurrence of and resistance to a certain class of diseases.

AN UNUSUAL CASE OF CEREBRAL TUBERCULOSIS FOLLOWING TUBERCULOUS OTITIS MEDIA.*

By H. O. REIK, M. D.,

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J. N., colored, three and a half years of age, was brought to the dispensary of the Baltimore Eye, Ear and Throat Charity Hospital April 5, 1909, with the following history: When about two years old his mother first noticed a purulent discharge from the left ear; there was no apparent preceding discomfort or febrile condition. The family physician was consulted but a profuse otorrhœa persisted in spite of treatment by irrigation and an operation, performed at one of the hospitals, through the external auditory canal, consisting probably, from the parent's description, in the removal of a polyp. In January, 1909, the child commenced to have muscular twitchings of the left side and spasmodic movements of the left leg and arm, followed by a growing inability to use these limbs. Such attacks recurred at irregular intervals, with increasing frequency, until on April 4 there was a pronounced convulsion; the spasmodic movements then involved the entire body but, the mother thought, began in the left leg and continued more pronounced on the left side; there was slight, if any, retraction of the head and the child made no outcry, though it was not completely unconscious. The attack began at 4 p. m. and lasted two hours or more, with short intervals of quiet. Suspecting a connection between the convulsions and the ear disease, the family physician advised sending the child to the hospital.

On admission, the child appeared to be of normal size but poorly nourished. He was perfectly conscious, rather apathetic, understood and obeyed simple questions and commands, and showed no irritation at the examination. The head was persistently held to the right but there was no retraction and no stiffness of the neck. Voluntary movements of the right leg and arm were freely made but he showed no inclination to move the left leg and, when the left arm was moved, supported it with the right hand. On manipulating the left leg or arm there was at first a feeling of limpness which at once gave way to a spastic condition in which extension and flexion of the joints seemed retarded, as if the joints were stiff. The left eye could be closed but there was a condition of lagophthalmos and when observed later, in sleep, the eye was partly open. Ophthalmoscopic examination showed nothing of importance; it was thought at first that there was a slight venous congestion but repeated examinations led to the conclusion that this was a mistake. The temperature on admission was subnormal, 97.5° F.

Before referring to the aural examination it may be well to present the notes of the neurological investigation made the following morning by Dr. Henry M. Thomas, who was kind enough to examine the patient for us. In brief, his report was

* Read before the Southern Section of the American Laryngological, Rhinological and Otological Society, Washington, D. C., February 12, 1910.

as follows: "Patient lies with the head drawn to the right but if turned to the left does not seem to suffer any pain. The neck is a little stiff but the head can be turned in all directions without giving any discomfort. Visual axes equal and ocular movements good. Pupils small but respond to light. Reflexes: Abdominal, active on right, present but not marked on the left. Cremacteric active on both sides but more marked on the left; tendon Achilles active on both sides but more so on the left; patellar active on both sides, suggestion of a clonus on the left; plantar stimulation causes response on both sides, as does also descending tibial pressure. Kernig's sign absent; Babinsky's and Oppenheim's negative. Diagnosis: Left hemiparesis with active reflexes."

Aural examination: Right ear perfectly normal. Left external auditory canal filled with pus that seemed to form almost as rapidly as it could be wiped away. The tympanic membrane and ossicles apparently completely destroyed and the tympanic cavity partially filled with granulation tissue. In the superior wall of the canal, close to the annulus, a fistulous tract from which pus could be seen oozing into the canal and pressure above the auricle, over the squamous portion of the temporal bone, increased this flow. The preauricular and supramastoidal glands were considerably enlarged and pressure over the antrum caused some little pain, though the tenderness was either not of high degree or the child was not in a very sensitive condition. Pus from the ear showed a mixed infection, pneumococci predominating, but a few streptococci and some bacilli that morphologically resembled tubercle bacilli were seen; with a special stain one slide showed what was believed to be a single specimen of the tubercle bacillus, but repeated efforts later, failed to produce more positive evidence of this and, unfortunately, cultures were not successfully grown.

The blood examination showed a leucocytosis of 12,500, in which the differential count gave 60 per cent of polymorphonuclear cells.

A lumbar puncture gave a perfectly normal spinal fluid; clear in color, under no pressure, and smears and cultures made from it proved negative.

The Calmette conjunctival tuberculin test was employed, with no resulting reaction.

There having been no recurrence of the convulsions and no markedly urgent symptoms the patient was kept under close observation for the next four days. During that time the temperature varied from 99° F. to 102° F.; there was no nausea and no apparent suffering; the principal symptoms were fever and a profuse discharge of pus from the ear.

From the above history and examination, it was apparent that we had to deal with a chronic suppurative otitis media, possibly of tubercular origin, which had certainly invaded the mastoid and probably the intracranial structures. An operation was certainly indicated but how extensive would it probably be? The fever, profuse discharge of pus, fistula in the external auditory canal and partial facial paralysis did not necessarily mean anything more than mastoiditis. The convulsions and the paretic condition of the left side were difficult to explain; the first might be due to a general septic condition accompanying mastoiditis or to an extradural collection of pus; the increased intracranial pressure produced by the latter lesion might explain the existence of both the convulsions and the paresis. Leptomeningitis was ruled out by the normal condition of the spinal fluid. A cerebral abscess was considered possible but there were no strong supporting symptoms; only once, at the time of admission, had the temperature been below normal and that was readily accounted for otherwise; a differential blood count did not indicate it; there were no localizing symptoms; the muscular impairment of the left side suggested a cerebral lesion on the side of the brain opposite the affected ear, but we have previously reported a case in which typical Jacksonian convulsions were caused by an extradural abscess of the same side. The only possible conclusion then seemed to be to perform a mastoidectomy and explore the base of the brain through this wound.

The operation was performed April 10 and proved very interesting. An incision through the soft parts was made slowly, layer by layer, as is our custom, and in this instance it was particularly well that the general advice, to plunge the knife down to the bone at once and make an incision completely through all the soft structures and the periosteum at one cut, was not followed for by so doing the brain would almost surely have been injured; in cutting the deeper subcutaneous tissues there was a sense of giving way before the pressure of the knife blade as though there was no bony support, and this was practically the case. When the soft tissues were retracted it was found that nature had done a fairly complete exenteration of the mastoid and that, in addition, there was a large sequestrum of the squamous portion of the temporal bone; the postero-superior bony wall of the canal and the superficial cortex of the mastoid, down nearly to the tip, had necrosed and were represented by a mass of dead tissue only; the sequestrum included the temporal ridge and the squama from above and measured 20 mm. square. Between this and the dura was a considerable collection of pus.

We had then a mastoiditis with extensive bone destruction and an extradural abscess, the margins of the abscessed area being completely walled off by inflammatory adhesion of the dura to healthy bone. Cleaning away the visibly diseased tissues, recourse to chisel or gouge being unnecessary, we found that the sigmoid portion of the lateral sinus was exposed as was also the tempero-sphenoidal lobe of the brain above, both on its lateral and under surfaces, the roof of the tympanum and antrum having completely disappeared. The area of exposed dura measured 25 by 35 mm. and it, as well as the sinus, had seemingly resisted the disease. During the investigation the sinus was injured and bled rather freely for a moment but the hemorrhage was promptly controlled by rapidly enlarging the opening in its bony wall, so as to permit the brain pressure from within to close the wound of the soft vessel wall.

It must be remembered that all this exposure of the dura and of lateral sinus, and the destruction of the postero-superior canal wall, the roof of the middle ear and antrum and the

FIG. 3.—External surface of right hemisphere. Superficial appearance of tubercular areas in the parietal lobe and antero-posterior section through tubercle of the temporal lobe.

FIG. 2.—Base of left hemisphere showing abscess cavity involving almost the entire tempero-sphenoidal lobe.

FIG. 1.—Section of spleen showing large areas of caseation.

FIG. 4.—Cross-section of the right hemisphere just posterior to the Rolandic fissure. Entire paracentral lobe destroyed. Tubercular destruction of the cortex of the posterior central and parietal convolutions.

complete exenteration of the mastoid process, was done by the disease and the operation consisted in doing little more than cleaning away the debris. The wound was lightly packed with sterile gauze from behind the auricle, the area being adjudged too large to attempt closure as in the ordinary so-called "radical" operation, and, because we thought it possible that further exploration of the brain might become necessary.

The immediate result of the operation was most satisfactory. The temperature dropped, with some irregularity, until it reached normal on the third day and there was a steady improvement in the general condition. At first the facial paralysis seemed to be somewhat increased and the child coughed a great deal but, possibly aided by the administration of syrup of the iodide of iron and careful feeding, these symptoms disappeared and he gained rapidly. There were no more convulsions, he began to take an interest in his surroundings, and gradually developed an inclination to use his left arm and leg, so that in the course of a few weeks he could walk and could use the left hand quite freely. The purulent discharge from the aural wound continued to some extent but he seemed to be on the road to complete recovery and on June 2, the local condition had so far improved that an attempt was made to close the post-auricular wound by a plastic operation.

This operation was successfully performed by my associate Dr. J. W. Downey. On June 21 the patient had a sudden rise of temperature to 103.5° F. and for the next ten days ran a mildly septic fever; the cause for this condition we could not determine. On the 1st of August his parents were permitted to take him home with the understanding that he should be brought to the hospital at least once a week for examination: there was still a slight discharge from the ear. He was not well cared for at home, however, and early in October was readmitted to the hospital ward, the ear being in a filthy condition from accumulated purulent secretions and with a fistula due to a partial breaking down of the scar tissue behind the auricle. A thorough cleansing and curettement was performed and he was soon making good progress once more. He had now recovered good use of the arm and leg and we had come to hope that he might be restored to perfect health, although he had occasional unaccountable rises of temperature.

From the 23d of October to the 12th of November his temperature was practically normal and then suddenly rose to 102° F. and he became listless and drowsy. The mastoid wound was reopened and the tempero-sphenoidal region again explored but nothing of importance was disclosed. Dr. John Ruhräh was kind enough to visit the hospital and examine the child for us. He found no evidence of pneumonia, a complication we had thought possible, and could only say that the condition was one of sepsis. At the next dressing of the mastoid wound, the septic temperature having continued, and the child being evidently critically ill, we decided to search the brain for an abscess although there were no clear signs of the existence or localization of such a lesion. A long narrow scalpel was passed into the tempero-sphenoidal lobe in various directions and a grooved director employed likewise, but no pus was obtained. The general condition gradually became worse and the patient died November 26.

An autopsy was performed within a few hours by the resident physician with the following results:

The heart was apparently normal. The lungs, unfortunately, were not as carefully examined as they should have been and for some unaccountable reason were not preserved; they were believed to be normal. The liver, spleen and brain presented very interesting lesions. These organs were preserved in a 5 per cent formalin solution and, later, Dr. Benjamin McCleary, of the College of Physicians and Surgeons, mounted the specimens and made sections for me.

The liver was found to be permeated with vacuoles of varying size, and Dr. McCleary's conclusion that this peculiar condition was probably due to infection by the gas bacillus was confirmed by Prof. William R. Stokes, State Bacteriologist.

The spleen contained two large areas of caseation, typical tubercles (Fig. 1).

The brain was, naturally, in view of the clinical history, the center of attraction and the specimen seems worthy of consideration. The dura was healthy looking, in the main, being but slightly adherent at several small points on the right hemisphere. The left hemisphere (Fig. 2) presented a large abscess cavity involving almost the entire tempero-sphenoidal lobe. The incisions made during operative explorations had passed directly through this cavity but the non-appearance of pus may be accounted for by supposing that the abscess had discharged itself through the middle ear.

The dura was easily stripped away from its points of adherence to the right hemisphere, disclosing yellowish, roughened areas, which, when incised, proved to be solitary tubercles. How extensive these were is well shown in the accompanying illustrations (Figs. 3 and 4). Cutting into the brain substance through the diseased-looking spots on the external surface exposed large areas of tuberculous caseation that involved the greater portion of the temporal and parietal lobes. Figure 3 shows the roughened appearance of the surface, posteriorly, and the deeper condition where an antero-posterior slice was removed from the surface of the temporal lobe. Figure 4 exhibits a cross section of the hemisphere, just posterior to the Rolandic fissure, with considerable destruction of the cortex of the posterior central convolutions, and almost complete destruction of the paracentral lobule on the mesial surface. Sections of these areas of caseation studied under the microscope show them to consist of typical tuberculous tissue.

Review.—It would seem probable that this was originally a case of tuberculous otitis media and that the mastoid disease and the cerebral abscess were direct sequellæ of this infection. It is possible, of course, though difficult to prove with certainty, that the cerebral tuberculosis of the opposite hemisphere was, likewise, the result of infection from the aural focus. The extensive destruction of brain substance in the motor region will explain the early paralysis of the limbs but it is not so clear why there should have been so marked an improvement in function after a mastoid operation of the opposite side. Solitary tubercle of the brain is a very rare condition, especially to such an extent as is observed here. How and why the meninges should have escaped in such a case is a mystery.

ETIOLOGY OF CHRONIC ARTHRITIS.

By Herman W. Marshall, M. D., Boston, Mass.

This subject, chronic arthritis, occurring as a complication of many diseases, cannot be explained in compact, easily comprehensible form; and attempts to simplify it are likely to fail. Moreover, positive proof of its causes is not within reach at present, and not likely to be attained soon, as will be explained later; therefore dependence must be placed upon theoretical statements which endeavor to harmonize pathological conditions with fundamental principles of chemistry, physiology, and bacteriology, and which are justified by improvements in clinical conditions of patients when they are followed in directing treatment. The working hypothesis presented below seems to fulfil these conditions.

Joint symptoms occur in constitutional, infectious and nervous diseases, and their causes are manifold, moreover, the various etiological elements do not act upon a simple tissue but upon a complex structure including bone, cartilage, connective tissue, nerves, synovial membranes, blood capillaries and lymphatics. The result of their action is seen in familiar pathological changes, bone atrophy and hypertrophy, cartilage destruction, periarticular fibrous thickenings and deposits, œdema, intracapsular fringes and synovial membrane changes, ankylosis, joint effusions; also symptoms of pain and stiffness.

Arthritis, therefore, must be conceded to be a complicated process if correct conception is to be obtained of it, and it is well to review the different ways by which joints may be influenced.

Most of the influencing factors may be grouped conveniently as follows:

I. Changes in quality and quantity of blood supply.
II. Disturbances of sensory and trophic nerves.
III. Mechanical factors of pressure and strains due to body weight.
IV. External physical influences, as variations in temperature, traumata, electricity, radiant heat, etc.

Through the blood stream come food materials and products from all body tissues, and occasionally in pathological conditions there are present abnormal products from diseased organs. When colonies of pathogenic bacteria establish themselves there appear in the blood of their host products of their cellular activities as from any group of tissue cells.

The chemical composition of the blood must be considered a highly complex one, due to various food materials, waste products of tissue metabolism, internal secretions, enzymes, pathological elements and toxins; and as the health of joints depends intimately upon the state of the blood, so the problem of joint disease deals with the delicate balance maintained by specially differentiated protoplasm of joint tissues to chemical, nervous, mechanical and thermal stimuli, that such protoplasm is ordinarily subjected to.

Variability in the vital resistance of joint tissues themselves, as well as differences in the various existing stimuli, should also be assumed and is in accordance with variations observed in all living tissues. Definite evidence of abnormalities originating in joints is seen in malignant new growths which occasionally develop there, and perhaps also in hæmophilic joints. The range of such abnormalities seems to be quite wide if clinical evidence be taken as an indication; and their assumed existence makes cases showing extreme pathological changes with very slight apparent causes more readily understood.

The theory, therefore, is proposed that *the causes of chronic arthritis are chemical irritants in the blood, disturbances of the central nervous system, mechanical pressures and strains, and external physical stimuli; and that each etiological factor may be a variable quantity, also that joint tissues themselves have a vital resistance of variable degree.*

Dependence of the Theory upon Clinical Data.

From a few selected patients whose clinical records have suggested probable causes with unusual clearness this hypothesis has been formulated which is of general application. The majority of patients, however, exhibit such confusing and slowly developing joint changes and have such indefinite clinical histories that they have been useless in the past for observation, and reliance has had to be placed only upon favorable instances of quickly developing, severe lesions which have followed and evidently were associated with causes equally well marked. When relationships have been once clearly defined then less obvious instances may be better interpreted through principles established in the undoubted ones.

Discussion of the Various Causes of Arthritis.

I. Irritating Substances in the Blood that may cause joint disturbances have the following sources:

a. Chemical products of bacterial growth.
b. Chemical products derived from gastro-intestinal tract.
c. Metabolic products of organ activities.
d. Therapeutic drugs, and poisons like lead.

I(a) Chemical Products of Bacterial Growth are well recognized causes of joint disease and enumeration of different infective foci seems superfluous. Blood examinations have repeatedly shown micro-organisms themselves associated with it. In chronic arthritis generally such examinations are negative, and these processes are due to products brought from a distant focus. In unusually severe, protracted instances bacteria find lodgment in joint tissues and have been demonstrated there exerting their toxic effect more potently.

Pathogenic bacteria produce various chemical substances, and among them toxins and ptomaines are of especial interest in the present connection.

Ptomaines are organic chemical compounds, basic in character, frequently of known composition and stable constitution, that are formed by the action of bacteria upon nitrogenous matter. Some are toxic and others inert.

Ptomaines are mentioned as possible causes of joint disease on account of severe arthritic cases which have recovered promptly after removal of fæcal impactions of the large intestine with enemata. Such patients have large numbers of spore-forming anærobic bacteria in the stools, and these bacteria form substances that are absorbed and appear in the urine: therefore suspicion rests upon excessive development of these comparatively harmless products, and they may be supposed to influence joint structures as the metabolic substances do that deposit sodium bi-urate in cartilage and connective tissue when present in blood in excess. Localization of the origin of arthritis in other cases by evidence furnished from operations upon the bowel help to support this suspicion. Some patients have had severe joint troubles clear up promptly and permanently after colotomies done for ulcerations of the rectum.

Toxins are organic chemical compounds, not generally basic in character, of unknown chemical composition and unstable constitution, that are formed by the action of bacteria upon nitrogenous food materials.

Vaughan and Novy state in their text-book upon Cellular Toxins that "poisons may be produced by the cellular activity of bacteria much in the same way as morphin is formed in the poppy," also that "it is now generally believed that most, if not all, of the pathogenic micro-organisms consist of cell walls containing protoplasm, and that the specific toxin is a constituent of the protoplasm, and that its formation is one of the vital phenomena manifested by the organism in its processes of growth and multiplication. In some species the cell wall is not easily permeable and the toxin is found only within the cell, while in other species the toxin formed within the cell readily passes through the wall and diffuses through the tissues when the germ is multiplying in the animal body."

The chemical nature of bacterial toxins is unknown because they have never been obtained in pure form. From the purest available preparations beliefs have been advanced that they are ferments, and again that they are albuminous bodies, but ignorance of their exact chemical structure must be admitted. That they are synthetic products has been demonstrated in some instances, at least, by cultivation of micro-organisms upon simple food substances from which they were able to elaborate complex toxins in the usual manner.

Gonotoxin is contained within the cell wall of the micro-organism, and filtrates through porcelain from fresh cultures are inactive. The toxin becomes freed only by disintegration of the organism.

Staphylococci form a soluble staphylolysin which acts upon red blood cells, also pyogenetic proteids may be extracted from cell contents of these organisms.

Typhoid bacilli contain within their bodies typhotoxin which is diffused upon disintegration of the bacteria.

Tubercle bacilli produce soluble toxins, and from liquid cultures DeSchweinitz isolated a crystalline body corresponding closely to teraconic acid to which he attributes the necrotic effects observed in tuberculosis. Koch was able to extract from bodies of tubercle bacilli two characteristic bodies belonging to the unsaturated fatty acids. Klebs obtained from them a nuclein, yielding 8% and 9% phosphorus after removal of the above mentioned fats. Glycerine water extracts of bacilli contain a mixture of substances some of which are proteid in character.

Bacteria also form ferments which probably play an important part in the production of morphological changes after the disease process has been inaugurated.

I(b) CHEMICAL PRODUCTS DERIVED FROM THE GASTRO-INTESTINAL TRACT should be considered the source of irritating substances in the blood, that cause joint lesions in a certain percentage of cases. Clinical evidence of complete recovery from severe arthritis by treatment of well marked intestinal disorders has been the experience of many observers, and the most convincing evidence of this relationship lies in the complete subsidence of arthritic symptoms following colotomies, by which the large intestine is emptied and temporarily put out of function. Complicated conditions exist in the digestive tract owing to presence of multitudes of bacteria which reside there, and live upon the food of their host; therefore for the sake of clearness comparison will be made of chemical changes in food proteids resulting from bacterial activity, and digestion of proteids by tissue cells of the digestive organs.

Through the agency of digestive ferments elaborated in the stomach, intestine and pancreas, food proteids are split into simpler bodies by hydrolytic cleavage. The simple nitrogenous end products are polypeptids, amido bodies, tyrosin, leucin, glutamic acid, a-pyrrolidin carbonic acid, aspartic acid, tryptophan, arginin, lysin and histidin. These comparatively simple substances are absorbed by the intestinal mucosa, enter capillaries of intestinal villi and pass to the liver where further changes occur, and finally appear in the general circulation uniformly as serum albumin, paraglobulin and fibrinogen. Ultimately they are distributed to body tissues by the blood, where they are built up into living protoplasm by intricate metabolic activities of tissue cells. Important changes therefore take place in the intestinal mucosa, liver, and at the cell walls of tissues where ultimate distribution occurs. Waste nitrogenous products enter the blood stream and are eliminated through the kidneys and other excretory organs.

Chemical changes in food proteids resulting from bacterial growth are similar to those observed in digestion as it is carried on by the tissue cells of the alimentary tract. Proteids are split by bacterial ferments into the same simple nitrogenous end products by processes of hydrolysis, but in addition bacteria carry their action further to formation of still simpler bodies. These simple nitrogenous end products of bacterial action are built directly into living protoplasm without mediation of special digestive cells of intestinal mucosa, and liver. Waste products from bacterial vital processes are eliminated directly instead of requiring special excretory organs.

Consequently the protoplasm of bacterial cells must be considered widely divergent from that of tissue cells, as in bacteria are condensed all the vital processes carried on by

stomach, intestine, liver, pancreas, and kidneys; and the metabolic products of bacterial activity must be considered to be distinctly different from products of tissue metabolism. Moreover, upon these differences which cannot be measured at present by existing methods of chemistry and physics, the toxicity of bacterial substances probably depends.

What the exact chemical grouping or physical constitution of substances is that makes them affect joints is not known, nor have all these bodies been identified. It seems certain that bacterial toxins and the antecedents of sodium bi-urate may influence joints, and suspicion rests upon bacterial ptomains and metabolic products from various organ activities.

It is the writer's belief that joint irritants may originate in the digestive tract from excessive numbers of spore-forming anærobic bacteria in the colon, also from tissue cells of stomach and intestine under pathological conditions independently of bacteria, similarly as toxic bodies are known to develop in association with demonstrable pathological states like cancer.

This belief cannot be positively proven, yet rests upon clinical evidence, for there are many arthritic patients whose only illness has been severe chronic dyspepsia, and whose arthritis has improved and grown worse with improvement and relapses of this trouble.

Immunity experiments of introducing foreign substances into the animal body, which lead to the production of protective anti-toxins show that tissues may adapt themselves by forming new substances in their protoplasm, and this remarkable capacity to vary according to requirements of health seems to make the idea more probable that occasional metabolic products are developed in pathological states of gastric and intestinal mucosa, as well as in other organs, that cause arthritis similarly as bacterial toxins produce joint disease. Goldthwait, too, has shown by means of X-rays taken after administration of bismuth subnitrate that arthritis is sometimes associated with displacements of stomach and colon, and that joints improve when abdominal viscera are supported with suitable pads.

This relation of visceral displacements to arthritis may perhaps be assumed to lie in mechanical interference with blood vessels and nerves supplying stomach and intestine, as well as stretching of the tissues, and that the resultant effect is a pathological condition of the lining epithelium of these organs. This pathological state of the epithelium leads to the formation of irritating substances in the blood that affect the joints; and by assuming that joint structures have variable resistances, an explanation can be given why all patients with enteroptosis do not have arthritis.

At present it is impossible to suggest all the pathological states of the digestive tract that lead to production of joint irritants, or to tell what combinations of chemical, nervous, mechanical and physical stimuli act upon the cells of the mucosa to cause their production, but the belief in their existence grows stronger as the number of patients observed grows larger. Whether there are many different substances formed in pathological conditions of the gastric and intestinal mucosa cannot be imagined. The cases that simply have chronic dyspepsia as a probable etiological factor, generally have hypertrophic bone changes which may perhaps indicate a different nature of the irritant from bacterial toxins as the latter lead usually to destructive atrophic changes.

I(c) Metabolic Products from other Organs seem to be the cause of arthritis also, if clinical data be accepted as evidence, and in profound changes going on during pregnancy and at the menopause many observers have noticed development or disappearance of severe joint symptoms. During pregnancy severe arthritis may show marked improvement but it usually recurs again when the uterus has passed through its involution stages. Arthritis may develop soon after pregnancy, and at the menopause, and the most probable explanation is an alteration in the chemical products which these organs supply to the blood. Similar relationships have been recorded between the joints and thyroid, spleen, pancreas and skin, but are less thoroughly established.

That a group of arthritic cases originates in toxic metabolic products of the blood derived from organs must be acknowledged to rest upon scanty data at present, and this paucity of data is due partly to comparative rarity of such disorders. The best established relationships are those of the joints to uterine and thyroid changes. Gout should also be grouped in this large class.

I(d) Therapeutic Drugs used in rheumatic conditions are generally administered to relieve pain. Salicylates circulate in the blood as alkaline salts and exert their effect mainly upon sensory nerves. Urotropin is excreted by synovial membranes as formaldehyde when it is given by mouth and is employed in cases of an infectious nature.

In cases of lead poisoning there are sometimes severe joint pains referable to the action of lead upon nerve cells when it is circulating in the blood.

Ether, circulating in the blood, may produce an unusually prolonged anæsthesia of articular sensory nerves. This fact strongly suggests a pathological condition of them; and indicates possibly the cause of the arthritic processes in such patients. All persons do not respond similarly and only those having very acute attacks exhibit the phenomena strikingly, yet in favorable instances the reaction cannot be mistaken. If a small amount of ether be administered to patients in the manner usually employed in surgical operations, until the patient has lost consciousness and the muscles have just relaxed, there will be upon recovery a sudden diminution of very excruciating pains previously complained of, and such joints exhibit surprising restoration of motion while the anæsthesia lasts. The effect usually lasts a day or so and may terminate the attack. In the few cases observed too profound narcosis or a repetition of it has seemed to cause less favorable results than the first primary anæsthesia, and unfortunately it cannot be generally used therapeutically. However, this property of ether may possibly have diagnostic value in such severe, comparatively rare cases. Discussion of the action of all drugs used in arthritic diseases is too extensive to be undertaken in this paper.

II. THE CENTRAL NERVOUS SYSTEM may have an important influence upon joints, as is well illustrated by destructive joint lesions occurring in tabes dorsalis and syringomyelia; and if clinical appearances are to be credited there are numerous attacks of arthritis which are initiated by nervous disturbances, and it should be remembered that nerve cells are subject to variations like all other tissues and are dependent upon the same variable states of the blood. An unusually sensitive nervous system acting upon joints of abnormally low resistance may be supposed to occur occasionally, and will account for some progressive cases which obstinately grow worse in spite of treatment.

In such individuals mental strain or prolonged worries destroy their nervous balance and the joints suddenly become affected. This action may not be a simple one in every case, for it should be remembered that all organs are under control of the nervous system, and that simultaneously there may be initiated digestive disorders together with joint troubles; certainly such cases are met with in practice which exhibit nervous symptoms, indigestion and arthritis.

The question arises in such instances, which is the cause and which the effect, because it is known that digestive products influence all tissues, including nerve cells, and that nervous stimuli undoubtedly affect digestive functions. It seems reasonable to suppose, and it is borne out by clinical histories, that sometimes one, and sometimes the other cause starts the trouble according to the relative vital resistance of nerve and digestive cells.

The nervous system accordingly may be supposed to influence joints directly through articular nerves or indirectly through other organs by setting up abnormal processes in them which result in irritants in the blood.

Pain in arthritic diseases may come from pressure upon nerves as they emerge through vertebral foramina and is then referred to regions irrespective of joints. Dull aches in joints sometimes are due to pressure upon terminal filaments of sensory nerves, yet perhaps in the majority of cases accompanied by incessant grumbling pains they express an underlying pathological process going on in the nerve cells which are abnormally weak, or which are being subjected to chemical irritants in the blood.

III. MECHANICAL IRRITATION TO JOINTS from pressure of body weight, occupation strains, and traumata are important and well recognized, and there are always factors of weight and motion to be considered regardless of the original causes, which may aggravate or perpetuate joint lesions after the initial cause has ceased to act.

Mechanical pinching of inflamed synovial membranes frequently results in the hypertrophied villi seen so commonly in operations. The pressure of body weight may continue arthritic processes associated with deformity simply by abnormal strains upon the affected joint structures; and there are so many cases of arthritis developing after traumata that no reasonable doubt can exist that this mechanical factor initiates the process in some instances.

IV. VARIOUS EXTERNAL PHYSICAL AGENCIES have been repeatedly recognized as etiological factors by clinicians; workmen who are subjected to extreme and rapid changes of temperature in foundries are supposed to be more likely to rheumatic affections; and women whose occupation requires continual irritation of hands from scrubbing or dipping into water frequently develop arthritis confined to these members. Probably in many such instances there is a true relationship between external causes and arthritic disease, at least in patients who have in their blood toxic substances likely to attack points of weakened resistance.

APPLICATION OF THE THEORY TO TREATMENT.

Many patients have been improved, and some of them have been completely cured of severe arthritis by keeping in mind the various etiological factors that have been enumerated; consequently this theoretical conception has proven to be of very practical value.

Treatment should consist in a search for the most probable underlying causes rather than in attempting to treat many possible origins in the same individual; moreover recognition that several causes often act together simultaneously, permits a better comprehension of the complicated conditions that frequently are observed.

Compulsory sedentary life of patients with severe joint disease tends to produce digestive disturbances and constipation with formation of irritating substances in stomach and intestine; and these may get into the circulation and prolong irritation in weakened joints after original causes have ceased to act. The importance of the digestive tract becomes obvious when consideration is given to the frequency of its disorders, and to the fact that its regulation is an important way of influencing the health of all tissues independently of any direct connection between it and joints. Simple modifications of diet, stomach washings, normal saline enemata, and supporting pads for relaxed abdominal walls have already been productive of very great benefit to arthritic conditions in selected cases.

Local therapeutic measures should be carried out thoughtfully; for example, immobilization of joints by plaster casts may cause rapid subsidence of symptoms and return of normal conditions in inflamed joints when the cause is mainly due to the mechanical irritation of motion and body weight; while in cases in which the origin lies in toxic substances of the blood such a procedure may permit the inflamed synovial surfaces to become adherent, and the joints to stiffen.

Thermal measures, as hot applications or bakings increase circulation locally and stimulate the protoplasm of cells. This may be beneficial in some instances, but when joint tissues are struggling with toxins in the blood that tax their resistance to the utmost, over-stimulation of the worn-out tissues is likely to happen, with a worse result finally than if these therapeutic measures had not been used. Such treatments should be mild at first and discontinued soon if no amelioration takes place, or continued cautiously only as long as symptoms improve.

It is only possible to suggest in this article how applications

of the working hypothesis which has been presented may yield an increased number of cures through careful consideration of each individual case instead of employing routine measures and drugs without thought of etiology of the disease.

Accordingly this working plan, although not fully established, seems the best method of treatment available at present, and it will probably be modified and elaborated as data are assembled from cases in which it has been applied. It has already proven useful, and, therefore, perhaps may be of sufficient general interest to warrant publication.

NOTES ON NEW BOOKS.

A Text-Book of Diseases of the Ear. By MACLEOD YEARSLEY, F. R. C. S. (*Chicago: Chicago Medical Book Co., 1908.*)

We recommend this work as one of the best written in the English language on this subject. It is simply and clearly written so that the beginner in otology can easily follow it and so comprehensive that the special worker in this field can learn much from it.

All of the chapters are so well written that it is impossible to praise one more than another. However, the author is to be congratulated for his additions to the usual routine chapters, namely, those on the influence of general diseases of the ear, aural reflexes, deafmutism and medico-legal and life insurance.

In discussing the surgical treatment of the contra-cranial complications of middle ear suppurations, the author lays stress on the foolishness of approaching these conditions, as so many surgeons do, by inaccurate trephining. The proper method is to lay bare the original seat of the disease in the middle ear or mastoid and follow the extension to the brain as can usually be done.

Throughout the book are many references, which though not exhaustive are very useful and interesting, in that they indicate the historical development of the subjects discussed.

Numerous original illustrations help to make clearer the various diseases and operations described.

SYLVAN ROSENHEIM.

The Pathology of the Living and Other Essays. By B. G. A. MOYNEHAN, M. S. (Lond.), F. R. C. S. Price, $2.00. (*Philadelphia and London: W. B. Saunders Company, 1910.*)

Those who have not read Mr. Moynehan's papers as they have appeared in the British Medical Journal and elsewhere will be glad to secure them in this form; and all students of surgery will find them well worth reading. In these essays the author presents the gist of his wide surgical experience, which, along the line of gastro-intestinal operations, has been surpassed by but few. He is a keen observer, of sound judgment, and his knowledge of the subjects he deals with so thorough that this small volume contains much more of real value than many larger volumes dealing with the same subjects.

The Expectation of Life of the Consumptive after Sanatorium Treatment. By NOEL DEAN BARDSWELL, M. D., M. R. C. P., F. R. S. (Ed.), etc. Price, $1.50. (*Edinburgh, Glasgow and London: Henry Frowde and Hodder & Stoughton, 1910.*) *Oxford Medical Publications.*

The author's work is well known to and appreciated by all students of the problems of tuberculosis, and his latest volume is one of exceptional interest, as such statistics as he furnishes are very scarce. Dr. Bardswell has followed his patients with care and diligence so that his figures are of more than ordinary value. After a brief introduction he describes the "Method of Classification Adopted," which conforms with that of the National Association for the Study and Prevention of Tuberculosis, and then gives a "Summary of Results of Treatment." This he follows with a "Commentary," and then concludes with "Life Histories" of patients under his care who had either "incipient," "moderately" or "far advanced" disease. Hardly any book on the clinical side of tuberculosis that has lately appeared has the importance of this study, which is admirably presented.

Consumption: Its Prevention and Home Treatment. A Guide for the Use of Patients. By H. HYSLOP THOMSON, M. D. Price, $1.00. (*London: Henry Frowde and Hodder & Stoughton, 1910.*) *Oxford Medical Publications.*

This small guide is a practical one and may be cordially recommended. In ten brief chapters the author discusses clearly The Causes of Consumption, How to Avoid Susceptibility, Precautions against Infection, The Necessity for Home Treatment, Requirements for Home Treatment, The Temperature and Body Weight, Personal Measures, The Importance of Routine in Treatment, The Diet of the Consumptive, and When to Seek Medical Advice.

Manual of Surgery. By ALEXIS THOMSEN, F. R. C. S., Ed., and ALEXANDER MILES, F. R. C. S., Ed. Two volumes. 3d edition revised and enlarged. Price $7.00. (*Edinburgh, Glasgow and London: Henry Frowde and Hodder & Stoughton, 1909.*) *Oxford Medical Publications.*

This book was reviewed in this journal in July, 1908, and there is only to be added that the authors have revised the sections on syphilis, serum and vaccine treatment, the surgery of individual nerves, the use of the Röntgen rays in the diagnosis of certain rare affections, etc. The first volume is devoted to general surgery, the second to regional surgery. The illustrations are plentiful, but not of fine quality. The print and paper are good and the volumes are of a comfortable size. The work is one of many useful surgeries, of which there is a superabundance, for medical students.

Burdett's Hospitals and Charities, 1910. The Year Book of Philanthropy and Hospital Annual. Twenty-first Year. Price, 10s. 6d. (*London: The Scientific Press Limited.*)

Each volume adds to the importance of this publication, to whose value attention has been frequently drawn. The immense amounts of carefully detailed statistics in regard to hospital, and other charity institutional expenses cannot be found in any other work. Comparison with expense accounts of American hospitals is almost out of the question, but all superintendents may learn much from a study of the reports furnished by Sir Henry Burdett. We wish that the trustees of the Russell Sage fund might see their way to publish a similar work for the United States.

U. S. Department of Agriculture, Bureau of Animal Industry.—Circular 153. (*Washington: Government Printing Office, 1910.*)

This circular on "The Dissemination of Disease by Dairy Products, and Methods for Prevention" has been well prepared. It is made up of five chapters, as follows: 1, Milk as a Carrier of Contagious Disease, and the Desirability of Pasteurization, by G. Lloyd Magruder; 2, The Importance of a Wholesome Milk Supply by John R. Mohler; 3, The Relation of the Tuberculous Cow to Public Health, by E. C. Schroeder; 4, Interpretation of Results of

Bacteriological Examination of Milk, by L. A. Rogers and S. H. Ayres; and 5, Pasteurization, Its Advantages and Disadvantages, by M. J. Rosenau. The papers, although brief, are concise, and set forth in a plain style matters of importance to all consumers of milk. These educational pamphlets issued by the different bureaus in Washington are one of the most valuable products of our government, and the work coming from the Bureau of Animal Industry deserves special commendation. We would urge all medical men to secure and study these reports which deal with the social welfare of the country at large.

Text-book of Hygiene. By GEORGE H. ROHÉ, M. D., and ALBERT ROBIN, M. D., etc. Fourth Revised and Enlarged Edition. Illustrated. (*Philadelphia: F. A. Davis Company, 1908.*)

The last edition of Rohé's Hygiene, edited by A. Robin, presents a number of interesting changes which make it more acceptable as a text-book for students and as a reference book for physicians. The subject material has been rewritten, mostly by well-known authorities in the various branches. Thus, Surgeon-General Walter Wyman has revised the chapter on Quarantine, Surgeon-Major McCaw, the one on Military and Camp Hygiene; Surgeon-Major Beyer, the one on Naval Hygiene, while Dr. Frances W. Upshur has edited the chapters on School Hygiene, Exercise, and Training, etc. Attention should be particularly directed to the section on Naval Hygiene, by Dr. Beyer. It is one of the best chapters in the book and one of the best small treatises on the subject of Naval Hygiene extant. The bacteriology of this book is much to be criticised. The information given is antiquated and even if it were up to date would be totally inadequate to the subject. In the analysis of water, for instance, slightly over two pages are given up to the bacteriological examination, while about ten pages are devoted to the chemical tests. Yet the bacteriological findings are admittedly more delicate and trustworthy than the chemical and will more certainly reveal a sewage pollution. Despite this fault, which runs through the whole book, it is a valuable and interesting volume on hygiene and should prove useful to sanitarians as well as to medical men. The value of the book would be much enhanced if the present editor would eliminate the foolish questions addressed to the reader at the end of each chapter. They create a superficial resemblance to a "quiz-compend" and have no place in so well written and scientific a book as the present edition.

Intestinal Auto-Intoxication. By A. COMBE, M. D. Together with an Appendix on the Lactic Ferments with Reference to Their Application in Intestinal Therapeutics. By A. FOURNIER. English adaptation by WILLIAM GAYNOR STATES, M. D. (*New York: Rebman Company, 1908.*)

In this work the author has presented in a very readable and instructive manner the diversified subject of intestinal auto-intoxication. His treatment of the subject is comprehensive and distinguished for the clear manner in which the various subdivisions are laid before the reader. The knowledge of the chemical processes which take place in the intestinal tract which is so necessary for the reader in order that he may clearly interpret the pathological physiology of intestinal auto-intoxication is briefly and well presented. Perhaps this feature of the work is the best.

A very interesting chapter is that dealing with the antitoxic functions of the body, in which are discussed:

1. The factors limiting intestinal putrefaction.

2. The triple line of defense surrounding the intestine, *i. e.*, the intestinal mucosa, the liver, and the antitoxic glands.

3. The elimination of intestinal poisonings.

Other instructive chapters are those dealing with the experimental pathology, diagnosis, and the symptomology.

A very large part of the work is devoted to the treatment of intestinal disorders, and here the author has helped the reader very greatly by organizing into a schema the rather confused knowledge that has grown up with the development of this special side of the subject. The discussion of the divisions of nitrogenous intestinal putrefaction, lactic ferments, the physiology and classification of yeasts contains much information of value. The volume is brought to a close with a chapter on stimulating the action of the antitoxic glands and the emunctories of the body, that is, the renal, cutaneous and intestinal emunctories.

The author acknowledges his use of the classical works of Strauss, Albu v. Jacksch, Charrin and Widal in his preface. This volume is an instructive and simple presentation of a rather complex subject, and has the especial merit of bringing into one work information that has been heretofore largely scattered through the literature.

Protozoölogy. By GARY N. CALKINS, Ph. D. Illustrated. (*New York and Philadelphia: Lea & Febiger, 1909.*)

The recent edition of Protozoölogy by Gary N. Calkins, Professor of Protozoölogy in Columbia University, New York, may be recommended not only to students of biology, who have a special interest in the study of the unicellular organisms but also to students of medicine, who are anxious to learn the relation of these organisms to disease in man and in the lower animals.

The book is based on the author's lectures on this subject in the Lowell Institute during the fall and winter of 1907. It is divided into 10 chapters illustrated with engravings and colored plates. The first chapter is devoted to morphology and classification, the second to physiology, the third to the life cycle, the fourth to conjugation, maturation, and fertilization, etc. In these chapters the author gives us a succinct account of the general principles, of forms, structure and function underlying our knowledge of the protozoan organisms. From the fifth chapter devoted to parasitism, on, through the concluding sections, the essentially medical side of the science is emphasized, and its bearing on the cancer problem and on such diseases as syphilis, small-pox, and scarlet fever is thoroughly reviewed. Both the Spirochaetae and the Trypanosomes are considered at length, and the method of transmission of protozoan diseases by insects is well presented. In the last chapter devoted to the pathogenic Rhizopoda, the etiology of dysentery, small-pox and rabies is treated of at some length, and the author presents the evidence in favor of the view which he possibly more than any other protozoölogist maintains; namely, that the Negri bodies stand in etiological relationship to rabies and the bodies described by Councilman in small-pox in the same position in regard to this disease. At the present time, possibly, this view is not entirely in harmony with the views of many protozoölogists nor with the views of the cytologists who are apt to look upon the various structures described in these affections as degeneration products or cell inclusions, which are not themselves the parasite, but may possibly harbor it.

Prof. Calkin's book is an excellent defense of the contrary opinion that these structures form in reality part of the life cycle of a protozoan organism, and on this account it deserves an especial study by medical men. It can be particularly recommended to those physicians who are apt to come in contact with the various infectious diseases of unknown origin, especially those seen in the tropics.

THE JOHNS HOPKINS HOSPITAL BULLETIN.

The Hospital Bulletin contains details of hospital and dispensary practice, abstracts of papers read, and other proceedings of the Medical Society of the Hospital, reports of lectures, and other matters of general interest in connection with the work of the Hospital. It is issued monthly.

Volume XXI is in progress. The subscription price is $2.00 per year in the United States, Canada, and Mexico; foreign subscriptions $2.50.

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Public Health Reports. Issued in weekly numbers by the Surgeon-General of the Public Health and Marine-Hospital Service of the United States. Volume 24. Part I. Numbers 1-26. January-June, 1909. 8vo. 938 pages. 1910. Government Printing Office, Washington.

Klinische Immunitätslehre und Serodiagnostik. Ein Lehrbuch für Ärzte. Von Dr. A. Wolff-Eisner. Mit 5 Abbildungen im Text. 1910. 8vo. 186 pages. Gustav Fischer, Jena.

New and Non-official Remedies, 1910. Containing Descriptions of the Articles which have been Accepted by the Council on Pharmacy and Chemistry of the American Medical Association, prior to Jan. 1, 1910. 12mo. 256 pages. American Medical Association, Chicago.

Handbook of Therapy. 12mo. 421 pages. The Journal of the American Medical Association, Chicago.

Proceedings of the Imperial Malaria Conference held at Simla in October, 1909. Fol. 107 pages. Government Central Branch Press, Simla.

Theoretical Principles of the Methods of Analytical Chemistry. Based upon Chemical Reactions. By M. G. Chesneau. Authorized translation by Azariah Thomas Lincoln, Ph. D., and David Hobart Carnahan, Ph. D. 1910. 8vo. 184 pages. The Macmillan Company, New York.

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Progressive Medicine. A Quarterly Digest of Advances, Discoveries and Improvements in the Medical and Surgical Sciences. Edited by Hobart Amory Hare, M. D., assisted by H. R. M. Landis, M. D. Volume 1. March, 1910. 8vo. 322 pages. Lea & Febiger, Philadelphia and New York.

The Propaganda for Reform in Proprietary Medicines. Containing the Various Exposes of Nostrums and Quackery which have Appeared in the Journal of the American Medical Association. Sixth edition. Illustrated. 12mo. 292 pages. Journal of the American Medical Association, Chicago.

International Clinics. A Quarterly of Illustrated Clinical Lectures and Especially Prepared Original Articles. Edited by Henry W. Cattell, A. M., M. D. Volume 1. Twentieth Series, 1910. 8vo. 301 pages. J. B. Lippincott Company, Philadelphia and London.

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The Surgery and Pathology of the Thyroid and Parathyroid Glands. By Albert J. Ochsner, A. M., M. D., LL. D., and Ralph L. Thompson, A. M., M. D. With 57 illustrations in the text and 40 full-page plates, 4 of the plates being in colors. 1910. 8°. 391 pages. C. V. Mosby Company, St. Louis.

La Tension Artérielle en Clinique. Sa Mesure. Sa Valeur Séméiologique. Par le Docteur Louis Gallavardin. 1910. 8vo. 206 pages. G. Steinheil, Paris.

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Diseases of the Stomach and Intestines. By Robert Coleman Kemp, M. D. With 280 illustrations, some in colors. 1910. 8vo. 766 pages. W. B. Saunders Company, Philadelphia and London.

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